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GONADOTROPIC HORMONE: COMPARISON OF ULTRAFILTRATION AND ALCOHOL-PRECIPITATION METHODS OF RECOVERY FROM URINE[1]

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TREATMENT of the hypogonadal patient, either male or female, cannot reasonably be instituted until a definitive diagnosis is established. The definitive diagnosis must state whether gonadal failure primarily involves the gonad or is secondary to failure of pituitary gonadotropin secretion. The only sure way to make this differentiation is to determine the amount of gonadotropic hormone in blood or urine.

If gonadal failure is secondary to pituitary failure, urinary gonadotropins will be distinctly lower than normal and stimulation by administration of gonadotropins is indicated. If gonadal failure is primary in the gonad, urinary gonadotropins will be distinctly higher than normal and administration of gonadotropins will fail to stimulate the gonad. Therefore substitutional therapy with sex hormones is permissible.

As yet methods for recovering and assaying urinary gonadotropins have been too complex, time-consuming and expensive for clinic and hospital laboratories, and as a consequence have been limited largely to research

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laboratories. Recently Gorbman (1) introduced a new principle for recovering urinary hypophyseal hormones by use of the ultrafilter, which appeared to offer the possibility of overcoming these difficulties. Therefore we compared ultrafiltration with the alcohol-precipitation-dialysis method of Heller and Chandler (4).

The two methods will be compared from the point of view of (1) complexity, (2) time consumed, (3) expense, and (4) quantitative recovery. Both methods were conducted as originally described (1 and 2). Twelve-hour overnight urine specimens were collected from patients presumed to have lower than normal, normal, and higher than normal titers of urinary gonadotropins. Urines from each patient were pooled, and equal amounts of the pooled urine concentrated by each of the two methods concurrently. The concentrates were assayed on 22–24 day old female Sprague Dawley rats, injecting once every twelve hours for six injections. Twenty-four hours after the last injection the rats were sacrificed and the uterine and ovarian weights used as the assay end-point.

(1) Complexity of the two methods may be compared from the following résumé of each:

In *ultrafiltration*, the urine is placed in a pressure filter and forced through a collodion membrane. When filtration is completed, the membrane, along with the protein hormone residue which has not passed through the pores of the membrane due to the large size of the protein molecule, is removed from the filter and placed in alcohol-ether solution in a centrifuge tube. The alcohol-ether dissolves the collodion membrane and at the same time precipitates the protein hormone. The solution is centrifuged, the supernatant poured off, and the residue repeatedly washed with alcohol-ether. After the last centrifugation, the residue is allowed to dry in the centrifuge tube. At the time of assay the dry precipitate is extracted with water.

In *alcohol precipitation*, the urine is precipitated with five volumes of alcohol; the supernatant liquid is decanted and the precipitate transferred to a centrifuge tube where it is centrifuged, washed with ether, and dried. The precipitate is suspended in water, transferred to a cellophane bag and dialyzed against running tap water. After dialysis the hormone-containing suspension is transferred to a centrifuge tube, centrifuged, and the precipitate discarded. The clear supernatant solution is transferred to a beaker where it is reprecipitated with five volumes of alcohol. This precipitate is transferred to a centrifuge tube, centrifuged, washed with ether, and dried. When desired for assay, the dried precipitate is extracted with water.

It is apparent that the alcohol-precipitation method requires more

materials and more manipulation than does ultrafiltration. With each manipulation or transfer from vessel to vessel, possibilities of loss or error are increased.

(2) Time consumption is compared in the following tabulation:

Ultrafiltration:	*Time-Hours*
a. Collect protein on collodion membrane by ultrafiltration	3
b. Dissolve membrane in alcohol-ether (protein is precipitated) and c. Wash 5 times with alcohol-ether	1
d. Extract with 6 cc. H_2O	1
Total	5
Alcohol-precipitation:	
a. Precipitate with 5 volumes alcohol	12–24
b. Decant, wash precipitate with ether, dry	5
c. Suspend in H_2O, dialyze	12
d. Centrifuge, reprecipitate supernatant with 5 volumes alcohol	12–48
e. Decant, wash precipitate with ether, dry	2
f. Extract in 6 cc. H_2O	1
Total	44–92

(3) Expense. The main items of expense with the *alcohol-precipitation* method are labor and alcohol. *Ultrafiltration* reduces the labor and eliminates the use of large volumes of alcohol.

(4) Quantitative recovery. Comparisons were made by conducting assays on urines from patients presenting a variety of syndromes. These are discussed separately below. The syndromes involved primarily the gonads in some instances, and primarily the pituitary in others. Both male and female subjects were chosen. There is reason to suspect that the ratio of follicle-stimulating hormone to interstitial-cell-stimulating hormone (ICSH, also called luteinizing hormone) is not constant from syndrome to syndrome. For example, if both methods recover equal amounts of FSH but unequal amounts of ICSH, then in a syndrome in which predominately FSH is excreted the two methods would recover approximately equal amounts of gonadotropic substances. If, on the other hand, urine containing predominately ICSH is analyzed, one method might recover much more gonadotropic substance than the other. Therefore it seemed important to include examples of as many syndromes as possible. A second reason for listing the results of the gonadotropin assays by syndromes is to illustrate the clear-cut differences that can be drawn between normal, hypoexcretion and hyperexcretion types.

NORMAL GONADOTROPIN EXCRETION

Normal men. Urines from nine men were compared, using six-hour and twelve-hour aliquots. Fifty separate assays were conducted. At the six-hour level, rat ovarian weights were indistinguishable from those of the uninjected controls. However, uterine weights were increased by using concentrates from each method. At the twelve-hour level, the alcohol precipitation and ultrafiltration methods elicited equal ovarian responses

TABLE 1. NORMAL GONADOTROPIN EXCRETION

Type of Subject	No. of Cases	Urine: Aliquot Hours	No. of Assays	Uterine Weight[1]		Ovarian Weight	
				Method		Method	
				Ultrafiltration	Alcohol-precipitation	Ultrafiltration	Alcohol-precipitation
				mg.	*mg.*	*mg.*	*mg.*
Normal Males	9	6	15	84	63	9.4	10.2
		12	35	99	89	22.9	20.7
Endocrinopathies	7	6	14	41	47	10.8	11.1
		12	19	53	100	13.5	19.4
Total	16	6	29	60	57	10.2	10.5
		12	54	81	92	19.0	20.3
Uninjected control rats[2]			62	Range: 17.2 to 60.3 Ave. 31.0		Range: 3.9 to 19.0 Ave. 10.7	

[1] Uterine weights are recorded after fluid has been expressed.

[2] Uninjected control rats were included with each series of assays conducted and serve as controls for Tables 2, 3, and 4 as well.

of approximately 20 mg., along with maximal uterine stimulation (Table 1). Thus one may conclude that the methods recover equal amounts of gonadotropic hormone from urine of normal men, and that each method is capable of detecting the hormone in six-hour aliquots.

Endocrinopathies associated with normal gonadotropin excretion. These included one case each of Addison's disease, Cushing's syndrome, adrenogenital syndrome, pseudohermaphrodism having bilateral ovo-

testes, myxedema, simple hirsutism, and pituitary gigantism. Thirty-three separate assays were performed.

The concentrates of the two methods were apparently of identical potency at the six-hour level, but assaying at the twelve-hour level revealed that alcohol-precipitation had recovered slightly greater amounts. The uterine response to six-hour aliquots was positive in some patients and negative in others, but in no instance did ovarian weight response occur.

The difference in ovarian response at the twelve-hour level seen in Table 1 is not as great as the figures seem to indicate, since several ovaries of less than normal weight were included in compiling the ultrafiltration data. A reduction in ovarian weight often follows administration of small amounts of gonadotropin, if the dose is sufficiently large to cause stimulation of ovarian function without causing an increase in size (3). The ovarian stimulation is reflected by the uterine weight increase.

Averaging the assays of normal men with the assays of the various endocrinopathies exhibiting normal gonadotropin levels, it is readily seen that the ultrafiltration method and the alcohol-precipitation method are equally effective in detecting normal gonadotropin titers in urine, in both six-hour and twelve-hour urine aliquots.

INCREASED GONADOTROPIN EXCRETION IN HYPOGONADAL SYNDROMES

Examples of several of the hypogonadal syndromes which are characterized by hypergonadotropic excretion were chosen for comparing the two methods.

1. **Menopause.** The urines of three women over forty years of age were studied by both methods and the elevated titers confirmed the diagnosis of menopause.

2. **Premature menopause.** In a woman, age 26 years, with a history of abrupt amenorrhea accompanied by menopausal symptoms, the diagnosis of premature menopause was confirmed by finding elevated urinary gonadotropin titers.

3. **Ovarian agenesis.** Four cases of ovarian agenesis were studied by the two methods, and each method revealed the high urinary gonadotropin titer present in this syndrome.

4. **Klinefelter's syndrome** (*prepuberal or puberal seminiferous tubule failure*).

The three cases of Klinefelter's syndrome studied by both methods showed uniformly high titers of gonadotropin excretion.

5. **Adult seminiferous tubule failure.** Three cases of adult seminiferous tubule failure revealed very high urinary gonadotropin levels by both ultra-

filtration and alcohol-precipitation. This confirmed the information obtained by testicular biopsy that the testis was primarily involved.

6. **Male climacteric.** The one case of male climacteric compared by the two methods showed distinctly increased urinary gonadotropin titers by each method, coincident with the symptoms characteristic of this syndrome.

The recovery of gonadotropins in the above-mentioned hypergonadotropic syndromes are compared in Table 2. A significantly higher recovery in the one, two and three-hour aliquots was obtained when concentration was performed by alcohol-precipitation. Less striking differences were

TABLE 2. INCREASED GONADOTROPIN EXCRETION

Type of Subject	No. of Cases	Urine: Aliquot Hours	No. of Assays	Uterine Weight		Ovarian Weight	
				Method		Method	
				Ultrafiltration	Alcohol-precipitation	Ultrafiltration	Alcohol-precipitation
				mg.	*mg.*	*mg.*	*mg.*
Hypogonadal syndromes	15	1	9	47	64	16.5	24.7
		2	9	77	101	17.8	45.1
		3	22	113	114	38.2	63.6
		6	32	103	100	60.0	62.6
		12	30	110	119	75.6	86.5

noted at the six-hour and twelve-hour levels. Maximal uterine weight response was attained at the three, six and twelve-hour dose levels by both methods.

It must be concluded that in hypergonadotropic syndromes under the conditions of the assay comparison, alcohol-precipitation consistently recovers a greater amount of gonadotropin than ultrafiltration. This difference may be explained by our recent observation that in the ultrafiltration process the pH of the urine directly affects the amounts recovered, whereas variations in pH do not materially affect the amounts recovered by alcohol-precipitation. Present indications are that the urinary pH must be 6.0 or lower for effective recovery of gonadotropins by ultrafiltration. The pH of some of the urines may have been above this figure and therefore caused loss of the active principle.

The important point illustrated by this table is that in the hypergonadotropic hypogonadal syndromes both ultrafiltration and alcohol-precipitation recover many times the amount of gonadotropic hormone found in normal urines. They therefore provide a means of differentiating elevated excretion of gonadotropic hormone from normal excretion.

DECREASED GONADOTROPIN EXCRETION IN HYPOGONADAL SYNDROMES

Examples of several of the hypogonadal syndromes which are characterized by hypogonadotropic excretion were chosen for comparing the two methods.

Prepuberal children are by definition hypogonadal until puberty is attained, and it is well known that until then gonadotropin excretion is negligible in amount. Five such children were chosen for comparison with normal adults.

TABLE 3. DECREASED GONADOTROPIN EXCRETION

Type	No. of Cases	Urine: Aliquot Hours	No. of Assays	Uterine Weight		Ovarian Weight	
				Method		Method	
				Ultrafiltration	Alcohol-precipitation	Ultrafiltration	Alcohol-precipitation
Hypogonadal syndromes	10	6	12	31.7	29.6	12.0	10.7
		12	13	17.6	30.9	10.4	11.1

Hypogonadotropic Eunuchoidism. One example of this syndrome was studied.

Anorexia nervosa. Two cases, one of each sex, were studied.

Artificial suppression of gonadotropin excretion by the administration of 5 mg. of diethylstilbesterol daily was performed in two cases. One with ovarian agenesis had elevated titers before treatment; the other, a pseudohermaphrodite, had normal titers.

In the 25 assays conducted at the six and twelve-hour levels no hormone was detected, irrespective of the method of concentration. Thus both methods are capable of distinguishing between hypogonadotropic hypogonadism and normal gonadotropic excretion.

ACROMEGALY

Three cases of acromegaly which were studied proved interesting in that one example each of decreased, normal, and increased gonadotropin ex-

cretion was discovered. In the patients with decreased and increased excretion, the methods agreed closely. In the third patient, alcohol-precipitation recovered hormone which was within the variation of the normal range, but the single test performed at the twelve-hour level by ultrafiltration detected none.

DISCUSSION

The data summarized in Figure 1 show that either method will sharply delineate the hypogonadotropic syndromes from normal, or syndromes having normal gonadotropin excretion. In turn, the hypergonadotropic syndromes can be sharply delineated from the other syndromes.

TABLE 4. ACROMEGALY

Type	No. of Cases	Urine: Aliquot Hours	No. of Assays	Uterine Weight		Ovarian Weight	
				Method		Method	
				Ultrafiltration	Alcohol-precipitation	Ultrafiltration	Alcohol-precipitation
Decreased	1	6	4	41	29	12.9	11.4
		12	2	19	18	9.4	8.4
Normal	1	12	3	40	56	12.0	12.0
Increased	1	6	4	86	116	75.4	88.4
		12	2	93	121	108.5	56.3

Terminology. The terms "gonadotropic hormone" and "follicle-stimulating hormone" have been used interchangeably to signify the material in human urine recovered by the various concentration methods. The term "gonadotropic hormone" actually includes all the factors (of which follicle-stimulating hormone is one) which stimulate the function or morphologic development of the gonads. Greep et al. (2), found that purified follicle-stimulating hormone produces ovarian morphologic development but does not cause the secretion of estrogen. The addition of interstitial-cell-stimulating hormone is necessary to produce the secretion of estrogen. In the light of these observations, when uterine weight stimulation is used as an end-point it then follows that both factors are present. Therefore, the term "follicle-stimulating hormone" is incomplete, whereas the term "gonadotropic hormone" satisfies the requirements.

Assay end-point. We have used both uterine and ovarian weights as assay end-points. At lower dose levels (six-hour urine aliquot of a normal person), uterine weight increase occurs without ovarian weight increase. At higher dose levels, ovarian weight increase, along with maximal uterine weight increase, is observed. Thus, by using both uterine and ovarian weights as assay end-points, the range of usefulness of the assay animal is increased. Instead of using arbitrary units, results are expressed as

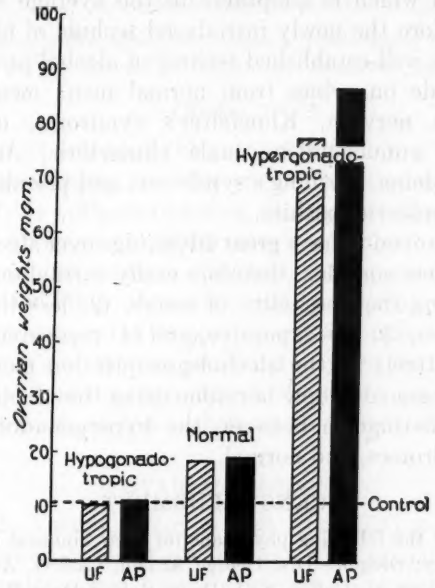

FIG. 1. Comparison of recovery of urinary gonadotropins by ultrafiltration (UF) and alcohol-precipitation (AP). Comparisons are compiled from the assays of twelve-hour urine specimens included in Tables 1, 2, and 3. The dotted line labelled "Control" is the average ovarian weight of uninjected control rats.

actual uterine and ovarian weights. This facilitates comparison and interpretation of the data by others.

When minimal or fixed organ weights (uterine or ovarian) are used as the end-point, and results described in terms of units, the organ weight becomes the constant, and the dosage of hormone or urine aliquot becomes the variable. This means that many dose levels and hence many assay animals must be used to arrive at the exact dose level which will elicit the arbitrarily chosen end-point. In contrast, by using the dose as the constant, and organ weight response as the variable, each assay animal yields definite information. In addition to the quantitative response,

qualitative information may be obtained by observing development of ovarian follicles, blood points, corpora lutea, and the stage of uterine development, estrogenic or progestational.

SUMMARY

Since gonadotropin determinations occupy a pivotal position in arriving at a definitive diagnosis in a variety of endocrine diseases, it is important to have a method which is adaptable to the average clinic or hospital laboratory. Therefore the newly introduced technic of ultrafiltration was compared with the well-established technic of alcohol-precipitation. Comparisons were made on urines from normal men, menopausal women, cases of anorexia nervosa, Klinefelter's syndrome, ovarian agenesis, hypogonadotropic eunuchoidism, male climacteric, Addison's disease, acromegaly, myxedema, Cushing's syndrome, and pseudohermaphrodism, as well as other endocrinopathies.

Ultrafiltration proved to have great advantage over alcohol-precipitation in that it was (1) less complex, therefore easily carried out by the average technician, reducing the possibility of errors, (2) less time-consuming (5 versus 44–92 hours), (3) less expensive, and (4) recovered almost as much hormone quantitatively as the alcohol-precipitation method.

By assaying for gonadotropic hormone using the ultrafiltration technic, one can readily distinguish between the hypergonadotropic and hypogonadotropic syndromes, and normal.

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THREE UNUSUAL ENDOCRINOPATHIES WITH ASSOCIATED OVARIAN PATHOLOGY: I. OVARIAN AGENESIS. II. PRECOCIOUS PUBERTY. III. VIRILISM[1]

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INTRODUCTION

THE ORIGINAL intent of the authors in grouping the following three dissimilar cases under one title was to emphasize the nonneoplastic ovarian origin of the endocrinopathies. It soon became apparent that the primary ovarian origin of the syndromes could not be upheld unequivocally. Nevertheless, inasmuch as the three cases present such a dramatic contrast, each to the other, it was thought appropriate to leave them as a triad: the first, an instance of congenital ovarian aplasia; the second, precocious hyperactivity of the ovarian function; and the third, a pathologic perversion of the same function. In all three the diagnosis was verified by surgical exploration, and in each instance benefit was obtained by appropriate therapy.

I. OVARIAN AGENESIS

In March 1942, Varney, Kenyon and Koch (31) published an article entitled, "Association of short stature, retarded sexual development and high urinary gonadotrophin titers in women; ovarian dwarfism." When they pointed out the association of either absent or at most rudimentary ovaries with this picture, they had introduced a new syndrome to the medical world. Thus was explained the mystery of the complete lack of response to pituitary gonadotropic hormones of many cases hitherto erroneously diagnosed as hypophyseal infantilism. In November of the same year, Albright, Smith and Fraser (1) further elucidated the same syndrome and carefully differentiated it from pituitary infantilism, or panhypopituitarism, as they choose to call it. Wilkins and Fleischmann (33), in August 1944, published a masterly exposition of the subject and gave the new syndrome its name, "ovarian agenesis." They analyzed and summarized the findings in the 47 cases thus far recorded in the literature,*

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* The 7 cases mentioned by Shereshevski (24) were not included in this tabulation.

of which 18 had been verified either by surgical exploration, peritoneoscopy, or autopsy.

As with all new syndromes, the next few years should see many more cases added to the series. The one which we are about to report represents the youngest thus far to be diagnosed and proved.

Case Record

L.L. (private patient, M.B.G.) was first seen in 1941 at the age of eight years because of failure to grow in height. All of her family were normal except for a maternal uncle who did not grow in height or mature sexually until his second year at college.

The patient was a full term baby and weighed 6 pounds at birth. She had 2 teeth before she was 4 months of age, and 16 teeth before she was 1 year of age. She had always been tiny and had been growing at an average rate of 1 inch per year. Otherwise her past history was not remarkable. Her performance at school had been average.

In appearance, this 8 year old girl had the facies and dimensions of a 5 year old (Fig. 1a). Her measurements at this time were as follows:

Height	42⅝ inches
Weight	45½ pounds
Span	41½ inches
Upper segment (pubis to vertex)	23⅛ inches
Lower segment (pubis to floor)	19½ inches
Ratio of upper to lower	1.18
Circumference—neck	11 inches
Circumference—chest	24¼ inches
Circumference—waist	23 inches
Circumference—abdomen	23½ inches

Her skeletal build was somewhat disproportionate in that the lower legs were quite short and unusually muscular. There were 12 permanent teeth present. All the teeth were small, the upper incisors seeming to incline lingually. The gingivae were unusually heavy. Otherwise the physical findings were not unusual. The osseous development was only slightly retarded, being estimated at between six and seven years. The roentgenograms of the skull were normal except for a slight underdevelopment of the clinoid processes. On ophthalmologic examination, the fundi were normal, as were the visual fields.

Laboratory data: The urine and blood were normal. The whole blood cholesterol was 137 mg.%. A basal metabolic rate was not attempted.

The diagnosis at this time was pituitary infantilism. The child was observed closely over a period of five years, during which her only regular therapy was adequate diet, vitamins, and desiccated thyroid in doses averaging .045 gm. daily, which seemed to be her tolerance dose. For a short period she was given oral enteric-coated pituitary substance, without noticeable benefit. Skull plates, bone age studies, and ophthalmologic examinations were repeated at regular intervals. The record of her growth can be seen on Chart I.

From July to September 1942, a trial of stilbestrol therapy was made. During these two months she grew ¼ of an inch in height, began to show breast development and to grow axillary and pubic hair. This therapy was promptly discontinued because of her age (10½ years), and all signs of beginning maturity promptly regressed.

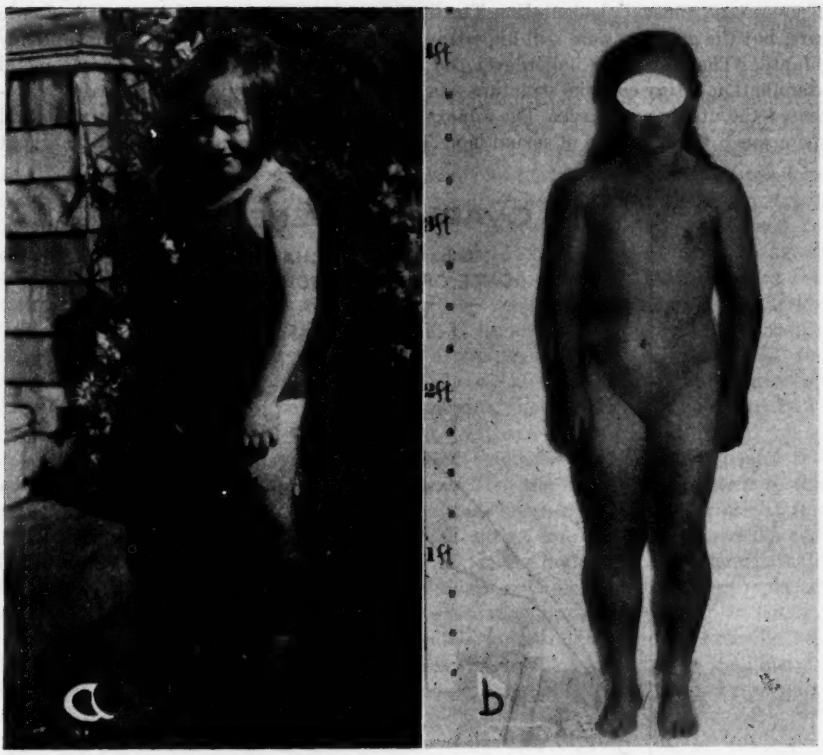

FIG. 1a. Age 8 years; height 42⅝ inches.
FIG. 1b. Age 12½ years.

Figure 1b represents the patient at the age of 12½ years. At this time she was a short, plump, alert, intelligent girl with the following measurements:

Height	49¾ inches
Weight	67¼ pounds
Span	51 inches
Upper segment (pubis to vertex)	25¾ inches
Lower segment (pubis to floor)	24 inches
Ratio of upper to lower	1.07
Circumference—chest, at nipple line	27½ inches

The span was relatively long for her height, whereas the lower extremities were short in proportion. The trunk was of childish configuration. There was no webbing of the neck or increased carrying angle of the arms (Turner's (30) syndrome). The hands and fingers were not remarkable. The musculature was normally developed. The subcutaneous fat was somewhat increased in amount, but uniformly distributed. The skin was of delicate texture, that of the lower extremities showing considerable purplish mottling.

There was no unusual pigmentation. The teeth were now quite normal due to orthodontic care, but the gingivae were still hypertrophic. The sexual development was completely infantile. The labia were underdeveloped and the clitoris was not enlarged. On rectal examination, a tiny cordlike structure was palpated in the midline. This probably represented the uterus and cervix. The adnexa were not felt. The breasts were infantile and there was a total absence of sexual hair. The osseous development, however, had kept

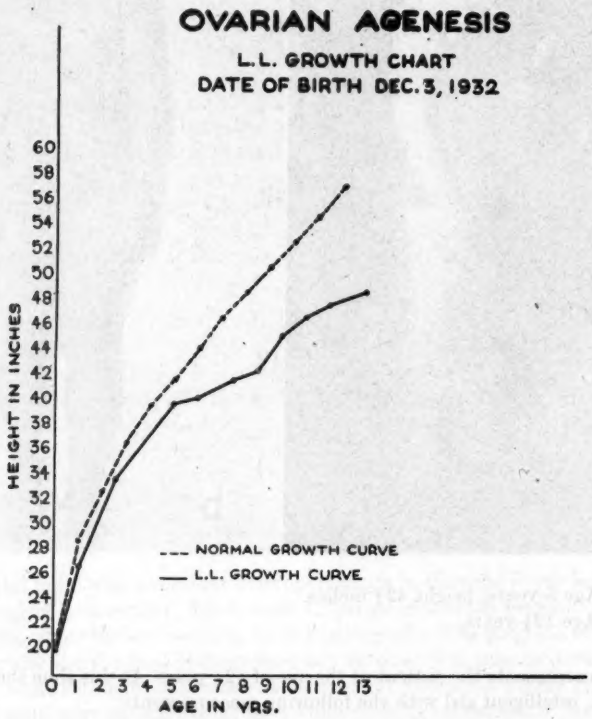

CHART I

pace with the passage of time, so that at the age of twelve and one-half years the bone age was estimated at between eleven and twelve years. The epiphysis for the external condyle of the humerus had begun to develop. The epiphyses for the trochlea and capitellum were ununited, as were those for the os calcis and for the olecranon. According to the illustrations of Todd, the development was approximately that of 10 years and 6 months. The skull and sella turcica were normal. Osteoporosis was not noted. The general physical findings were quite normal. The blood pressure was 100/75. The mental development seemed average and the child did fairly well at school.

Laboratory data: The urine and blood were normal. The basal metabolic rate was minus 11 per cent. The twenty-four hour output of 17-ketosteroids in the urine was 1.3 mg. The normal range for this age is 1.5–6 mg. per 24 hours (Talbot). The urinary

gonadotropin assay was between 27.2 and 40.8 mouse units per twenty-four hours (high for this age).

Although absence of secondary sex characteristics in a girl 12½ years old certainly should cause no concern, the association here of stunted growth, complete infantile appearance, and high urinary gonadotropin titer, suggested that this patient might be a case of ovarian agenesis. Albright and his co-workers (1) stress the fact that the osseous development in these girls is only slightly retarded and that fusion of the epiphyses does occur in due time. On this basis, it should logically follow that any therapy directed toward the production of linear growth must of necessity be instituted early enough to allow for sufficient growth prior to epiphyseal closure. If, however, the therapeutic agent so employed simultaneously produces development of secondary sex characteristics, the optimum time for beginning treatment should be about the normal age of puberty. The patient had already had a therapeutic test of stilbestrol for two months at the age of 10½ years. She had responded with a spurt of growth as well as beginning sexual development. Therefore prompt verification of the diagnosis seemed desirable in order that precious time would not be wasted, and surgical exploration was made January 4, 1946.

Operative report: The abdomen was opened through a midline incision and the pelvic organs exposed. Filmy adhesions extended from the fundus of the uterus to the upper portion of the bladder. The uterus was undeveloped; its greatest width at the site of the tubal insertion measured 1.5 cm., its length 2 cm., and its thickness 0.5 cm. The tubes were infantile and markedly convoluted; the fimbriated ends were patent. The most striking feature was the absence of ovaries. These structures were replaced by narrow streaks of glistening, greyish-white tissue, approximately 3 cm. in length, 0.4 cm. in width, and 0.3 cm. in thickness, which showed no evidence of follicular activity. The appearance of this tissue was so characteristic and so similar to the illustrations of Wilkins and Fleischmann (33) that no biopsy was taken. A scarred appendix was removed.

Subsequent course: Nine days postoperatively, January 13, 1946, therapy was begun with oral stilbestrol, 0.5 mg. daily for three weeks, followed by a rest of one week. This was a deviation from our usual course which consists of 42 mg. of stilbestrol monthly, given as follows: 1.0 mg. daily for the first week, 2.0 mg. daily for the second week, and 3.0 mg. daily for the third week, with a rest interval of one week. The smaller dose was prescribed because production of withdrawal bleeding was not contemplated. Surprisingly, however, this dose was not small enough to prevent withdrawal bleeding from a uterus which, less than five weeks previously, was observed to be completely rudimentary. During the second month the dosage of stilbestrol was cut in half (5.25 mg. in three weeks). Withdrawal bleeding again occurred. The dosage was then reduced to 0.1 mg. daily for twenty-five days each month, and withdrawal bleeding continued to occur cyclically each month even on this small dose. After five months of therapy, the patient had grown 1.0 inch in height. There was considerable increase in the size of the nipples and areolae, and axillary and pubic hair had begun to develop. The uterus and cervix were still tiny. Our goal at that time was to produce maximum growth with minimum sexual development.

Comment: Although the effect of estrogenic therapy on the development of secondary sex characteristics and the production of withdrawal bleeding, when given cyclically, is well known, much interest hinges, in this case and others like it, on the increment of growth which may be

achieved thereby. The average height to which these girls grow is 55 inches. Will estrogenic therapy, given in time, improve on nature's results?

II. PRECOCIOUS PUBERTY

Case Record

M.L., a six-year old girl, was brought to one of us (M.B.G.) December 9, 1943 for consultation because of vaginal bleeding of eleven days' duration. The mother reported that the child had not been feeling well for several weeks and had lost her appetite. She had complained, November 28, of left-sided abdominal pain with some radiation down the left leg. That evening slight vaginal bleeding was noted and this continued, necessitating the use of two pads per day for the ensuing eleven days. The mother had noted the presence of some pubic hair about three weeks before, but had been quite unaware of beginning breast development. The child was described as a bright pupil, but rather irritable and quick-tempered. The family history is of interest for the following points: The mother had three pregnancies of which the first was normal. That child is living and well, age 13 years, the menarche having occurred at the age of 12½ years. The second child died of a blood dyscrasia at the age of two days. The third pregnancy (the patient) was complicated by nausea and vomiting throughout the nine months, but the child was born apparently normal and well. The mother was ill for about four years following this delivery, the major difficulty being a severe hypotension. The father is living, but is beginning to develop some type of neuromuscular difficulty involving one upper extremity. The maternal grandfather was diabetic. One maternal cousin menstruated at the age of 9 years.

The early development of this child was normal. She weighed 7 pounds and 4 ounces at birth, and she teethed, walked and talked at the normal times. At two years of age she developed pyelitis. This was followed by measles and recurrent pyelitis. Following the measles she developed diplopia, and strabismus was then noticed for the first time. At 3½ years of age she was quite ill with chickenpox, although no undue lethargy or somnolence was noted. She had tonsillitis, otitis media and cervical adenitis, for which an adenotonsillectomy was performed at the age of 5½ years (July 1943).

Figure 2a is a photograph of the patient at the age of six years. Her measurements were as follows:

Weight	59½ pounds
Height	47¾ inches
Span	47¾ inches
Upper segment	24 inches
Lower segment	23¾ inches
Ratio of upper to lower	1.01

The child, when first seen, was tall for her age, well-developed, well-nourished and well-proportioned. She was somewhat unusual looking, due to the prominent frontal bosses and elongated mandible, giving an appearance suggestive of hydrocephalus. The scalp hair was abundant and normal in texture. There was an excessive growth of long hair on the forearms and legs, a slight amount on the pubis, but none in the axillae. The skin was soft, warm and smooth, but showed a definite tendency toward keloid formation. There were two small, flat, pigmented moles on the right side of the chest anteriorly, and one posteriorly. Dark shadows were present under the eyes. There was a bilateral internal strabismus, for which glasses were worn. The pupils reacted normally.

The fundi were normal. Perimetric studies were attempted but were unsuccessful. The dentition was normal for her age, as were all of the oral structures. The tonsils were absent. Small, shotty cervical lymph nodes were palpable bilaterally. The thyroid was normal. The breasts showed considerable rounding, and glandular tissue was definitely

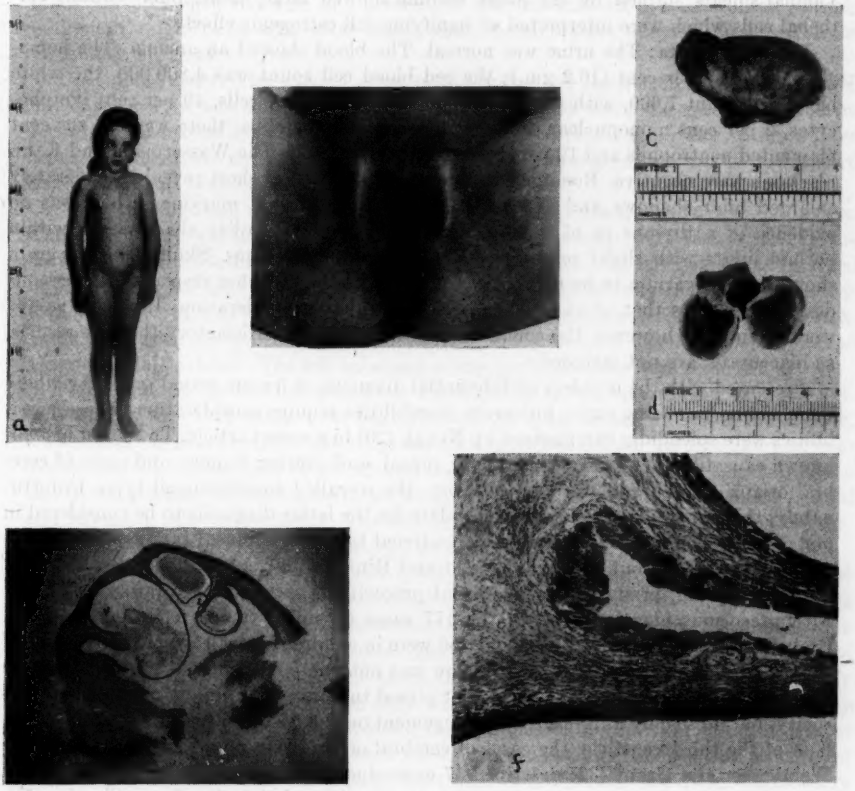

Fig. 2a. Age 6 years; height 47¾ inches.

Fig. 2b. Note pubic hair and excessive labial development.

Fig. 2c. Cystic left ovary.

Fig. 2d. Appearance of left ovary on section.

Fig. 2e. Microscopic appearance of left ovary (×45).

Fig. 2f. Margins of three cysts: upper and lower lined by a thin layer of unluteinized granulosa cells; center lined by a thick layer of luteinized granulosa cells (×120).

palpable. The areolae were pigmented and showed increased development, as did the nipples. The heart and lungs were normal. The blood pressure was 100/60. The temperature was 99.6° orally. The abdomen seemed full, but no organs or masses were felt. On the left knee there was a shiny, raised, hypertrophic scar, about 1 cm. in diameter. The reflexes were hypoactive, the biceps and triceps not elicited. There were no pathologic

reflexes. The genitalia were moderately overdeveloped (Fig. 2b). The clitoris was hooded but not enlarged. Both labia majora and minora showed excessive development. The hymen was seen to pout, and bleeding was present. On rectal examination the whole pelvis seemed to be occupied by a large uterus. Nothing else could be felt. Vaginal smears stained by the Shorr technic showed large, clear, pink staining epithelial cells which were interpreted as signifying full estrogenic effect.

Laboratory data: The urine was normal. The blood showed an anemia. The hemoglobin was 71 per cent (10.2 gm.); the red blood cell count was 4,800,000, the white blood cell count 7,600, with 48 per cent polymorphonuclear cells, 49 per cent lymphocytes, 2 per cent mononuclear cells and 1 per cent eosinophils; there were 88 per cent filamented neutrophils and 12 per cent nonfilamented cells. The Wassermann and Kahn reactions were negative. Roentgenologic examination of the chest revealed moderately enlarged hilar shadows and slightly increased peribronchial markings. There was no evidence of a thymus or of a mediastinal shadow. The cardiac shadow was within normal limits with slight prominence of the pulmonic regions. Skull roentgenogram showed the calvarium to be rather thick, but normal in all other respects. The osseous development was that of an eight-year-old—two years' acceleration. Hormone assays were attempted; however, the collection of urine was so unsatisfactory that the results, as inaccurate, are not included.

Presented with the problem of differential diagnosis of female sexual precocity where there are no localizing signs, numerous possibilities require consideration. These possibilities were splendidly summarized by Novak (20) in a recent article. To the list of well-known causative factors such as adrenal, pineal, and ovarian tumors, and cases of cerebral origin, Novak added a new category, the so-called constitutional type. Unfortunately, this paper appeared a month too late for the latter diagnosis to be considered in our patient. The possibility of either an adrenal tumor or a pineal tumor seemed most remote. As pointed out by Reilly, Lisser and Hinman (22), adrenal tumors are nearly always virilizing, producing pseudosexual precocity in girls, and are rarely associated with precocious menstruation. Of the 177 cases of pineal tumors collected by Bing, Globus and Simon (3) up to 1938, only 56 were in children under 15 years of age, and of these 21 showed pubertas praecox. There was not one female in this group. Since the evidence is accumulating to suggest that pineal tumors *per se* do not cause sexual precocity, but do so only as a result of impingement on the posterior hypothalamus and the floor of the third ventricle, the cases of cerebral origin came up next for consideration. Weinberger and Grant (32) described 17 cases due to tumors of the hypothalamus. Of these, three were females. Other lesions such as hydrocephalus (Dorff and Shapiro (7)), encephalitis, and measles encephalomyelitis (Ford and Guild (9)), have been described as producing sexual precocity. Of the 544 instances of pubertas praecox, other than those due to pineal tumors, collected by Bing, Globus and Simon (3), 13 of the verified cases had cerebral lesions and 51 of the 440 clinical cases had histories of involvement of the central nervous system.

The possibility that our patient belonged to this group had to be weighed on the basis of her barely-suggestive hydrocephalic appearance, and the strabismus. The Albright syndrome came in for brief notice, only to be eliminated as none of the associated characteristic findings were present, namely, osteitis fibrosa cystica or disseminata, and cutaneous pigmentation. An ovarian origin for the sexual precocity seemed most likely, despite the lack of palpable evidence. In the 104 verified cases of Bing, Globus and Simon (3) 42 (40 per cent) were due to ovarian tumors. When it is considered that the 104 cases represented both sexes, the percentage of ovarian tumors as a cause of female pre-

cocity becomes more impressive. On the other hand, the incidence of granulosa-cell tumors as a cause of sexual precocity is not as frequent as we have been led to believe. Lull (18), up to 1941, was able to find only 16 such cases in the literature.

Because of the rapid development of the syndrome in our patient, the abdominal pain, relatively prolonged bleeding and anemia, it was felt that an ovarian tumor, possibly malignant, might be present. With this in mind an exploratory operation was performed December 17, 1943.

Operative report: The vaginal canal readily admitted the length of a finger. A well developed cervix was sounded for a distance of one inch from the external to the internal os; the uterus measured 7.5 cm. (3 inches). The cervical canal was readily dilated to size #8 Hegar. No endometrium was obtained by curettage, which was to be expected as the child had been bleeding for nineteen days.

When the abdomen was opened, the uterus was found to be the size of an adult organ. The right ovary was small (1.5 by 0.5 by 0.5 cm.). No cysts were seen or felt in the cortex; the corresponding tube was infantile in appearance. The left ovary was enlarged (4.5 by 2.5 by 2.0 cm.) and showed evidence of much follicular activity; the organ was soft, yellow, with many small, bluish cysts, 4 to 5 mm. in diameter, lying in the cortex, and a large cyst, 2.0 cm. in diameter, occupying the outer pole. The left tube resembled a normal adult oviduct. The left tube and ovary, and appendix were removed.

Pathologic report: The left ovary was 4.0 to 2.2 by 1.8 cm. in size (Fig. 2c). The surface was smooth and white with numerous bluish cysts apparent below the surface. On section, the small cysts in the outer cortex were 0.2 to 0.5 cm. in diameter and contained clear, colorless fluid (Figs. 2d and 2e). At a deeper level was a larger cyst, 2.0 cm. in its greatest dimension, with an irregular outline, also containing colorless fluid and having a pale yellow lining. The left fallopian tube was 3.5 cm. long and 0.5 cm. in diameter in the ampulla. It resembled a normal adult tube.

Microscopically most of the small cysts in the ovary were lined by two or more layers of granulosa cells; a few were lined by theca interna cells (Fig. 2f). The theca interna around these cysts was moderately vascular; small groups of theca cells were rounded and contained small vacuoles. The larger cyst was lined by a thick layer of large luteinized granulosa cells. The theca interna was vascular; its cells were mostly spindle-shaped, but in small groups they were rounded and vacuolated. The primary follicles and follicles in the early ripening stages appeared normal; the ovum in a later ripening stage was degenerated. There were numerous atretic follicles but no corpora lutea. In the fallopian tube, the mucous folds were thin, delicate, and divided into many small branches. The epithelium was high columnar and the cells were crowded. Pathologic diagnosis: follicle cysts of the left ovary with one cyst showing marked luteinization; adult type ovary and tube; ovarian hyperfunction.

Subsequent developments: The child made an uneventful recovery except for keloid formation in the abdominal scar. All signs of precocious sexual development gradually regressed and no further bleeding occurred. When the patient was seen July 23, 1945, at the age of seven years and eight months, nineteen months postoperatively, she showed the following: height, 53 inches, an increase of 5¼ inches; weight, 72½ pounds; blood pressure, 90/60; pulse, 98. The child looked well, the strabismus was less evident, and the breasts and genitalia had regressed completely. The uterus and cervix were small, there was no pubic or axillary hair, the remaining ovary was not enlarged and the vaginal smear showed infantile type cells. Due to an intervening vacation period, followed by a prolonged febrile illness diagnosed as primary atypical pneumonia, photographs were not taken and urinary gonadotropic assays were not secured at this time. The child was

not seen until February 7, 1946, twenty-six months postoperatively. She had grown an inch and a half in a little more than six months. She looked pale and was nervous and fidgety. Signs of beginning maturity were again perceptible: slight development of breasts and growth of vulval and pubic hair and slightly increased development of the labia but not to the same degree as prior to operation. The uterus and cervix were not palpably enlarged and no bleeding had occurred. The urinary gonadotropin titer was not increased, being negative for 9.4 mouse units, the lowest level tested. Urinary 17-ketosteroids were 4.0 mg. per twenty-four hours.

Because of the possible cerebral origin of the syndrome and especially on account of progressive development of peculiar personality traits, encephalography was recommended but refused by the family.

Discussion: The finding of a unilateral polycystic ovary as the cause of precocious puberty was a little surprising to us. In a survey of the literature, by no means complete, we have noted only three other such cases: a 22 month old child reported by Lull (18), a 4½ year old girl by Fischer (8), and a 5 year old girl by Mengert (19). The latter case remained well for a follow up period of three years following extirpation of the cystic ovary.

In our case the ovarian pathologic changes might have been caused by an intracranial lesion, although its unilateral character, the regression of the symptoms postoperatively, and lack of recurrence for at least two years seems to speak against it. Furthermore, in all the proved cases of sexual precocity associated with lesions of the third ventricle or of the hypothalamus, no such changes have been reported in the ovary. A large cystic ovary did occur in one case of Albright's disease but no luteinization was observed, Sternberg and Joseph (28).

Finally the question arises as to what relationship this case bears to the nine reported by Novak (20), in which not only precocious bleeding occurred, but ovulation as well. Seven patients of his series were laparotomized; and of these three had unilaterally enlarged ovaries showing follicular cysts. Is our patient a representative of this group, merely with more pronounced cystic changes in the ovary? Had Novak's article been available to us at the time of operation, we might have been content to take a biopsy and allow the ovary to remain *in situ*. Our conjecture would be, however, that this child would then have continued to have prolonged episodes of bleeding, rather than normal regular periods, and would have subsequently required surgical intervention.

III. VIRILISM

Case Record

V.McD., age 18 years, was first seen by us (A.F.M. and M.B.G.) in January 1945, because of primary amenorrhea. Her mother had matured relatively late, age 16 years, and her menses had always been irregular; her only pregnancy was complicated by hypertension and toxemia.

The patient was an eight month premature baby who weighed 4 pounds 11 ounces at birth. Until her seventh year she was very delicate, having many respiratory infections and several bouts of prolonged and unexplained fevers. After her seventh birthday she began to improve in health, though she remained somewhat delicate and underweight. She was always small, the smallest in her class, and when sixteen years of age wore size nine clothes. At this time sugar was noted in the urine, but since a fasting blood sugar determination was normal this finding was discounted. Acne had been present since the age of thirteen to fourteen years. In 1943, between the ages of sixteen and seventeen years, the patient was treated for amenorrhea for several months at a time with courses of triweekly injections of estrogens in oil, in doses of 10,000 I.U. The patient knows that she grew very rapidly in the year, and her breasts began to develop, but she thinks that the beginning breast development and spurt in growth antedated the estrogenic therapy. Be that as it may, a few months following the institution of treatment, she noticed a sudden development of excess hair on face and body. Medication was stopped in November 1944. The patient claims that there has been no increase in the hypertrichosis since that time. Polyphagia and some polydipsia had been noted for two months. Large amounts of urine were passed at a time, but there was no nocturia. Perspiration was not excessive, although the patient felt warm. Mentally she was quite alert and intelligent and had an excellent memory. Though usually calm, she had been quite irritable for the preceding few months. She did not suffer from headaches.

Figures 3a and b are photographs of the patient, age eighteen years and three months. Her measurements were as follows:

Weight	118 pounds
Height	66½ inches
Span	66 inches
Upper segment (pubis to vertex)	32½ inches
Lower segment (pubis to floor)	34 inches
Ratio of upper to lower	.96

She was a slender, pale, odd-looking young girl with an excessive growth of coarse, blonde, facial hair extending along the cheeks, down under the chin, and onto the neck. There was, in addition, hair on the upper lip, a masculine pubic escutcheon, hair about the areolae, and long, coarse, wiry hair on the forearms and lower extremities. Extensive acne was present on the face and back. The eyes were wide-set and prominent, although the lid apertures were narrow. Ophthalmoscopic examination revealed normal fundi; the visual fields were normal. The dentition was normal except for the absence of one lateral incisor which had been extracted. The chest was quite narrow and the entire figure somewhat boyish, although there was some development of the breasts. The lungs were normal. The heart was not enlarged. There was a rough systolic murmur heard at the mitral area which was not transmitted. The pulse was 76 and the blood pressure 110/70. No organs or masses were palpable in the abdomen. The hands were slender and tapering and showed a coarse tremor on extension. The lower extremities were not remarkable and the reflexes were normal. Pelvic examination showed well developed labia and slight enlargement of the clitoris. The uterus and cervix were small. The ovaries were bilaterally enlarged to about the size of small hen's eggs and were firm to palpation.

Laboratory data: The urine was normal except for the frequent presence of a yellow precipitate when tested with Benedict's solution. The blood showed: hemoglobin, 94 per cent (13.6 gm.), 4,600,000 erythrocytes, 7,400 leukocytes; the differential smear showed: 68 per cent neutrophils, 28 per cent lymphocytes, 2 per cent monocytes, 2 per

cent eosinophils; filamented neutrophils were 87 per cent, nonfilamented, 13 per cent. The color index was 1.02. The basal metabolic rate was minus 2 per cent. The glucose tolerance test on January 23, 1945 was as follows:

	Blood sugar	Urine sugar
Fasting	93 mg.%	neg.
½ hour	206 mg.%	neg.
1 hour	253 mg.%	2 plus
2 hours	333 mg.%	4 plus
3 hours	233 mg.%	4 plus

Urinary hormone determinations revealed: twenty-four hour output of 17-ketosteroids (ketonic fraction) 21.1 mg. (normal 5.6 to 9 mg.); twenty-four hour output of gonadotropins, follicle-stimulating hormones (F.S.H.), 34 mouse units (normal); the combined estrogen level was reported as moderately low (exact figure not available). Vaginal smears, stained with Shorr's trichrome stain, showed definite evidence of estrogenic activity. Roentgenogram of the skull revealed the sella turcica to be normal in size and contour. The calvarium was moderately thin and uniformly calcified, showing no defects. Intravenous pyelograms showed no evidence of adrenal enlargement.

Clinical diagnosis: virilism with primary amenorrhea, uterine hypoplasia, hypertrophy of the clitoris, heterosexual hypertrichosis, impaired carbohydrate tolerance, and bilaterally enlarged ovaries, but without obesity, hypertension or plethora.

Pathologic differential diagnosis: (1) ovarian hyperthecosis (most likely); (2) bilateral arrhenoblastoma; (3) adrenal rest tumors of the ovary; (4) adrenal cortical hyperplasia or possibly adenoma. Pituitary basophilism was considered unlikely.

A pelvic exploratory operation was performed February 26, 1945.

Operative report: The abdomen was opened through a midline incision, and the pelvic organs exposed. A small uterus of normal contour, two inches in length, was pulled to the left of the midline by a dense fold of peritoneum which extended from the upper portion of the bladder to the left infundibulopelvic ligament; the right broad ligament was thereby stretched. The ovaries presented the following interesting features: both were enlarged and resembled the smooth "oyster-like" polycystic structures described by Stein et al. (25, 26); both were unusually firm to palpation; they were gray but innumerable small telangiectatic blood vessels coursing through the cortex suggested considerable vascular congestion; the right ovary was slightly larger than the left and measured approximately 6 by 5 by 3 cm. There was no evidence of follicular activity. The tubes showed normal adult development. Because of the bilateral involvement of the ovaries it was thought advisable to remove the excessive tissue and to restore the normal contour. A wedge-shaped resection was done on the right side

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FIG. 3a. Age 18 years; note hirsutism and acne.

FIG. 3b.

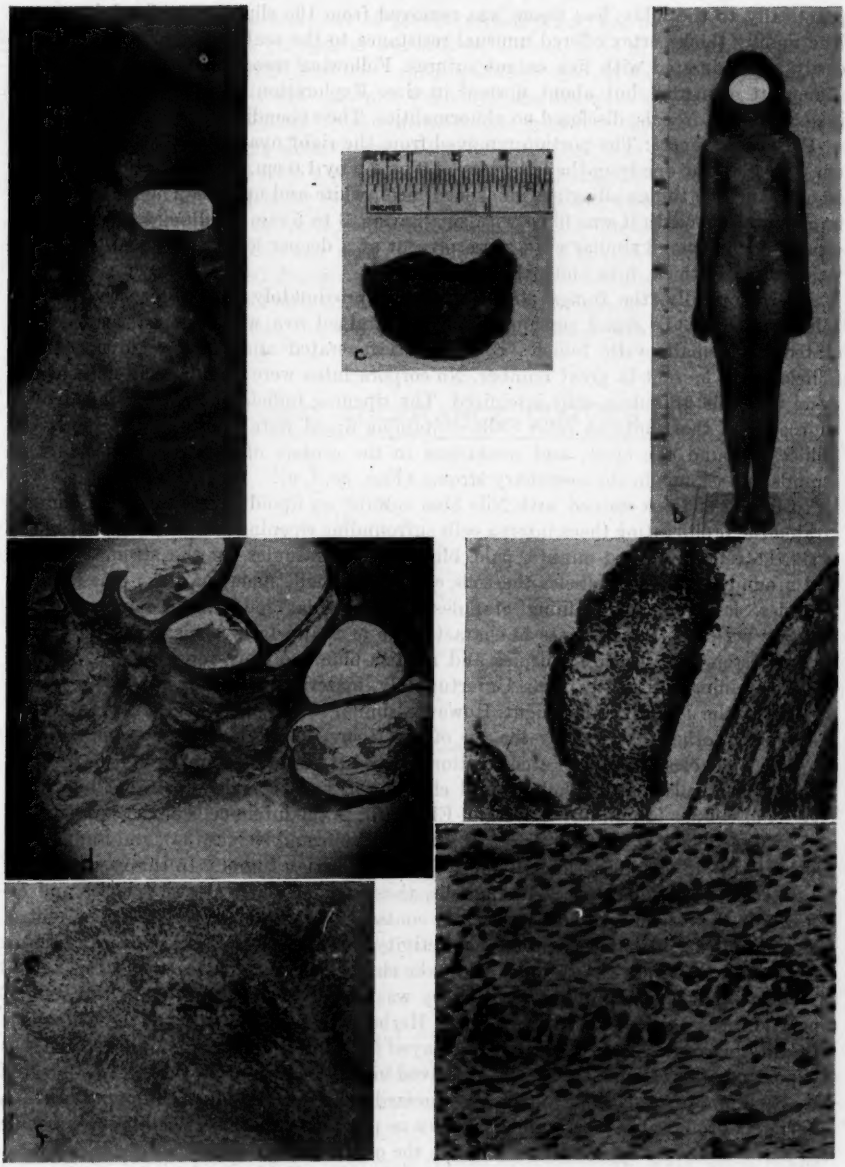
FIG. 3c. Resected portion of right ovary. Note cystic structure.

FIG. 3d. Ovary with follicle cysts in the cortex; thickened stroma with many atretic follicles (×30).

FIG. 3e. Follicle cysts lined with unluteinized granulosa cells; hyperplastic luteinized theca interna (×120).

FIG. 3f. Atretic follicle with central and peripheral masses of luteinized theca interna cells (×120).

FIG. 3g. Strands of luteinized theca interna cells in the ovarian stroma (×500).



FIGS. 3a–3g—See opposite page for description.

practically to the hilus; less tissue was removed from the slightly smaller left ovary. The unduly thick cortex offered unusual resistance to the scalpel. The cut edges were easily approximated with fine catgut sutures. Following resection, both ovaries were somewhat elongated but about normal in size. Exploration of the upper abdomen, including the adrenals, disclosed no abnormalities. The appendix was removed.

Pathologic report: The portion removed from the right ovary was 4.5 by 2.5 by 2.0 cm. (Fig. 3c), the one from the left ovary, 4.0 by 2.5 by 1.0 cm. The cortical surface was smooth and the tunica albuginea thickened, firm, white and opaque. The cortical layer immediately beneath it was filled with small cysts, 3 to 5 mm. in diameter, containing clear fluid; scattered similar cysts were present at a deeper level. The medullary part was unusually thick, firm and pale yellow.

Microscopically, the tunica albuginea was approximately three times the normal thickness (Fig. 3d). Small ripening follicles contained ova whose nuclei were degenerated, and small cystic follicles contained degenerated and collapsed ova. Atretic follicles were present in great number. No corpora lutea were seen, and in none of the cysts were the granulosa cells luteinized. The ripening follicles were surrounded by a wide zone of theca interna cells. Cells containing lipoid were found around the larger follicles, around the cysts, and sometimes in the centers of atretic follicles and in strands and islands in the medullary stroma (Figs. 3e, f, g).

In frozen sections stained with Nile blue sulfate, no lipoid substances were demonstrated the proliferating theca interna cells surrounding ripening follicles, but around the cysts the cells contained minute, pale, blue-staining granules. In the stromal strands and around the atretic follicles the cells contained small, spherical, deep-blue-staining granules, larger purple-staining granules and irregular red-staining clumps. Blue-staining with Nile blue sulfate is characteristic of soaps, fatty acids, cholesterol, cholesterol esters and lecithin, purples and reddish-blue probably representing mixtures of blue-staining and neutral fats. Unfortunately, material was not available for identification by the use of polarized light. However, similar small spherical granules have been identified in other material, by the use of the Hoerr-Romeis staining technic as phospholipid or cholesterol. That a correlation exists between hormonal activity and lipid content, particularly phospholipid and cholesterol, has been demonstrated by Bloor, Okey and Corner (4), and by Boyd and Elden (5), in the lutein cells of the sow's ovary, and by Greenblatt, et al., (15), Traut, et al., (29), Wolfe and Neigus (34), and Banner and Dockerty (2), in certain hormonally-active human ovarian tumors. In this case it should be noted that the older theca lutein cells, those around older atretic follicles and especially in the stromal strands, apparently contained a fairly large percentage of neutral fats, an indication that their hormonal activity was slight or absent. Ponceau-fuchsin staining failed to show the granules said to be characteristic of androgenic cells.

The resected portion of the right ovary was placed in butyl alcohol at the time of operation. It was subsequently sent to Dr. Herbert Evans' laboratory, at the University of California in Berkeley, where it was assayed for androgenic activity. The extract was evaporated at 56° C. and the residue dissolved in 2 cc. of sesame oil. One cc. was injected into each of two 21 day old hypophysectomized male rats six days postoperatively. No effect was produced on the seminal vesicles or prostate, indicating the absence of male sex hormone in any appreciable amount in the ovary.

Subsequent developments: April 3, six weeks after the surgical intervention and without any other treatment, the patient had her first menstrual period. These have since recurred at fairly regular intervals and have been characterized by normal flow with a duration of four to six days. Dysmenorrhea occurred on two occasions. The psy-

chologic effect of the establishment of normal menstruation has been dramatic. There have been no perceptible changes in the breasts, clitoris, labia or uterus. The acne is slightly improved while the hirsutism, though still present, is somewhat diminished, the hair being of definitely finer texture. Carbohydrate tolerance seems to have shown a steady improvement (Chart II). A glucose-insulin tolerance test, October 26, 1945, was interpreted as showing some degree of insulin resistance. The 17-ketosteroid assay of the urine had dropped from a preoperative level of 21.1 mg. to 16.8 mg. six months postoperatively, but March 30, 1946 had risen to 18.5 mg. per twenty-four hours (normal range 5.6 to 9 mg.). In April 1946 urine was sent to the laboratory of Dr. Herbert M. Evans for gonadotropin assay with partition of the F.S.H. and I.C.S.H. (interstitial cell stimulating hormone) fractions. Hypophysectomized female rats were injected with 120 cc. equivalent of urine. Neither follicular development nor repair of interstitial tissue was produced. The same amount was injected into hypophysectomized

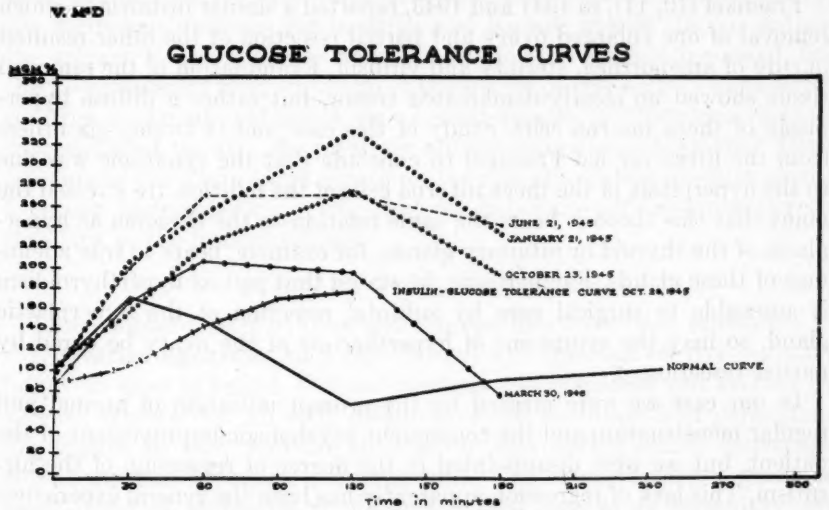


CHART II

male rats with no effect on seminal vesicles or prostate. It was concluded, therefore, that there were less than eight hypophysectomized rat units of either F.S.H. or I.C.S.H. fractions per liter of urine.

Discussion: Stein and Leventhal (26), in 1935, first insisted that the symptom complex of menstrual irregularities, notably amenorrhea, sterility, and varying degrees of defeminization or masculinization, in association with bilaterally enlarged cystic ovaries, constituted an endocrine syndrome. Up to 1945, Stein (25) had reported a series of sixty such cases, all treated surgically by ovarian wedge resection. In every instance this form of therapy resulted in the establishment or reestablishment of normal menstrual cycles and, in a significant percentage of cases, in the cure of

sterility. Stein and Leventhal (26), in 1935, stated that the only consistent pathologic change was the presence of follicle cysts lined by theca cells, while Stein and Cohen (27), in 1939, observed that luteinization of theca interna cells was the characteristic finding. Apparently, however, they did not consider these pathologic changes significant. They theorized that the polycystic changes in the ovary without corpus luteum formation were probably caused by an endocrine disturbance primarily hypophyseal, but that the resulting amenorrhea and sterility were caused by mechanical crowding of the ovarian cortex by cysts which interfered with the normal maturation of graafian follicles. It is on the basis of release of pressure that they explained the curative effect of ovarian wedge resection.

Fraenkel (10, 11), in 1941 and 1943, reported a similar instance in which removal of one enlarged ovary and partial resection of the other resulted in cure of amenorrhea, sterility and virilism. Examination of the removed tissue showed no clearly-demarcated tumor, but rather a diffuse hyperplasia of theca interna cells. Study of this case and of twenty-six others from the literature led Fraenkel to conclude that the syndrome was due to the hyperplasia of the theca interna cells of the follicles. He stressed the point that this thecosis bears the same relation to the thecoma as hyperplasia of the thyroid or pituitary glands, for example, bears to true adenomas of these glands. Furthermore, he stated that just as hyperthyroidism is amenable to surgical cure by subtotal resection of the hyperplastic gland, so may the symptoms of hyperthecosis of the ovary be cured by partial resection.

In our case we were pleased by the prompt initiation of normal and regular menstruation and the consequent psychologic improvement of the patient, but we were disappointed in the degree of regression of the hirsutism. This lack of regression apparently has been the general experience. At first we attempted to explain the results on the basis of persisting pathologic ovarian tissue, analogous to the situation where insufficient hyperplastic thyroid tissue is removed in hyperthyroidism. However, this explanation is untenable when one considers another group of cases, two reported by Geist and Gaines (12), two by Rottino and McGrath (23), and one by Cutting et al., (6), where bilateral ovariectomy was done and where little improvement in the signs of virilism ensued. Another explanation, therefore, must be forthcoming.

Normally, during the ripening of the follicle the theca interna cells proliferate and their cytoplasm becomes granular; a faint lipoid reaction can be demonstrated in them in the very early stages of corpus luteum formation. As the corpus luteum begins to degenerate, fatty acids appear in the cells of the theca interna. However, when a follicle undergoes atresia, the ovum and the granulosa cells perish, but the proliferation of

the theca interna cells continues. The proliferation is radial and eccentric and the cells, which contain fat at an early stage, become scattered among neighboring stroma cells.

Study of the microscopic pathology of our case leaves us with the impression that some factor as yet unidentified led to the premature death and degeneration of the ova, and that it is the increased amount of follicle atresia which accounts for the hyperplasia of the theca interna cells, most of which, on the basis of lipoid staining reactions, might be said to be hormonally inactive. Geist, et al., (13), and Greenblatt (14) showed that gonadotropins might produce this picture. Groher (16) demonstrated that androgens will stop development of normal follicles in immature female mice and that the follicles which developed prior to the administration of the androgens undergo degeneration and become atretic. In our patient the urinary F.S.H. titer was normal, the I.C.S.H. was not increased, but the 17-ketosteroid level was high. If the source of this high 17-ketosteroid titer lies in the adrenal cortex, as we must assume, is it intrinsic there or is it mediated through the pituitary-adrenocorticotropic hormone? These are some of the unanswered questions, the final elucidation of which awaits a clearer understanding of the intricate pituitary-adrenal-gonadal relationships in the human subject.

SUMMARY AND CONCLUSIONS

Three nonneoplastic ovarian endocrinopathies have been reported.

I. **Ovarian Agenesis.** An 8 year old girl was observed for five years for failure to grow in height. Ovarian agenesis was suspected and verified by surgical exploration. An early diagnosis of this condition is of paramount importance so that valuable time is not lost during which epiphyseal closure renders linear growth impossible. The extraordinary potency of small doses of stilbestrol in producing development of secondary sex characteristics and withdrawl bleeding has been demonstrated. Sufficient time has not elapsed to evaluate the growth-producing effect of the drug in this case.

II. **Precocious Puberty.** A 6 year old girl with precocious sexual development and vaginal bleeding was thought to have an ovarian tumor despite lack of palpable verification. At laparotomy a unilaterally enlarged polycystic ovary was removed with prompt regression of all signs of precocity. After twenty-six months of remission, signs of ovarian activity again became perceptible. The possible cerebral origin of the syndrome is admitted. Encephalography was recommended but refused by the family.

III. **Virilism.** An 18 year old girl with primary amenorrhea, heterosexual hypertrichosis, slight enlargement of the clitoris, acne and impaired carbohydrate metabolism was found to have bilaterally enlarged ovaries.

Urinary assays showed high 17-ketosteroid and normal F.S.H. values. Ovarian hyperthecosis was suspected. A bilateral partial resection of the enlarged, firm ovaries was done with prompt establishment of normal menstrual function, improvement in the carbohydrate metabolism, and some regression, but not disappearance, of the hypertrichosis. The gross and microscopic pathologic changes are discussed. The patient's subsequent course corroborates the conclusions of both Stein (25) and Fraenkel (10, 11) that the treatment of choice at the present time is partial ovarian resection. It seems doubtful that the hyperplasia of the theca interna cells is of primary etiologic significance. The final elucidation of this syndrome awaits a better understanding of the pituitary-adrenal-gonadal relationships and the histogenesis and functions of the several ovarian cell types.

In conclusion, we believe that special emphasis should be placed on the psychologic aspects of these cases. The importance of making each one of these girls as nearly normal as possible for her age scarcely needs to be be mentioned. Far-reaching psychologic trauma can thus be averted. In the first case, although fertility is out of the question, normal or near normal stature and secondary sex characteristics will make possible a normal life. In the second case, early psychologic trauma due to being different from other children, and the remote danger of early impregnation were obviated, while in the third case the personality changes which resulted from the mere establishment of the normal menstrual function were little short of a miracle.

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PAROXYSMAL HYPERTENSION WITH CONCOMITANT SWELLING OF THE THYROID DUE TO PHEOCHROMOCYTOMA OF THE RIGHT ADRENAL GLAND. CURE BY SURGICAL REMOVAL OF THE PHEOCHROMOCYTOMA

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THE CLINICAL picture, pathology and treatment of tumors, originating from the chromaffin tissue of the adrenal medulla (pheochromocytoma), or from the genetically and morphologically identical chromaffin tissue adjacent to the sympathetic chain (paraganglioma), and their symptomatology, the suprarenal sympathetic syndrome, is well known today, Belt and Powell (7), Wells and Boman (46), and Howard and Barker (25).

The case we are about to report is unusual since the patient presented a symptom hitherto not described in the literature, i.e., paroxysmal swelling of the thyroid gland, accompanying and simultaneous with paroxysmal hypertensive crises. Furthermore, there were extremely rapid and excessive variations in blood pressure, which usually are not associated with the syndrome.

In 1934 Belt and Powell (7) reviewed the sixty cases already reported in the literature, and simultaneously presented a case of their own in which the pheochromocytoma, weighing 1000 gm. and containing 2 gm. of adrenalin per 100 gm. of tissue, replaced the right adrenal. In the same year Bauer and Leriche (4) reported the sixth surgically-cured case of a chromaffin tumor. This tumor was a paraganglioma situated close to a normal left adrenal gland. During the last decade the number of diagnosed and successfully-treated cases has risen considerably. Up to 1939, 103 chromaffin tumors were recorded, either diagnosed or found at necropsy, Brunschwig and Humphreys (12). Of these, 43 were found in the right adrenal, 34 in the left adrenal, 13 in both adrenals, and 13 were situated entirely outside the adrenal glands. In 1942, Kirshbaum and Balkin (27) collected 116 cases. In 1943, Hyman and Mencher (26) found a total of 35 surgically-treated cases of chromaffin tumor reported in the world's literature. Four of these were paragangliomas not involving the adrenal glands. The operative mortality in this series of 35 cases was 5. The tumor was malignant in only one patient who later died of metastases.

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Case Report

Mrs. B. B., 47 years old, housewife, was first seen May 26, 1945, by one of us, Bauer. For approximately two years she had been suffering from spells which lasted from five to ten minutes. At first the spells occurred every seven to ten days, and later became far more frequent. Finally she had several attacks each day, occasionally even at night. The attacks may be described as follows: the patient felt slight pain in the stomach, in the legs, and arms; she then developed nausea and felt a swelling in her neck anteriorly; her heart began to pound, she shook and experienced extreme weakness and fatigue; her skin became very pale, then red; her lips and fingernails became blue. After such an attack she perspired freely and felt tired and weak. The swelling in her neck persisted for at least one-half hour. The attacks usually occurred after breakfast but might occur any time, especially when she was fatigued. She lost seven pounds in weight during the two years following the onset of the attacks.

The patient was always healthy, her only illness being measles, in childhood. She was frequently constipated. Her tonsils and adenoids were removed at the age of 17 years. The menstrual cycle began at the age of 17 years; menstruation was regular and without abnormality. She had two children.

In her present illness the patient consulted several physicians. A heart specialist and an allergist found nothing abnormal. One rhinologist wanted to puncture a paranasal sinus, but another was against it. Another physician considered her to be neurotic. Later she was treated with theelin for menopausal disorders. Finally the patient's physician, Dr. Marian Goldwasser, observed her during an attack and noted that the systolic blood pressure rose within a few minutes from 110 to 200. This observation induced Dr. Goldwasser to refer the patient to Dr. Bauer.

Family history: The patient's mother died at the age of 48 years of diabetes mellitus. Her father died at the age of 76 years of unknown cause. One brother died at the age of 47 years from diabetes mellitus. Another brother, 62 years of age, is diabetic. Two brothers are living and well. One sister died at the age of 26 years following childbirth. Another sister is living and well at the age of 54 years.

Physical Examination: The patient was of normal body build; was 61 inches tall and weighed 127 pounds. She had prematurely grey hair. On routine examination, the pulse was 80, and the blood pressure 120/80 to 130/88. The thyroid was not enlarged. The lungs, heart, abdomen, and nervous system, did not show any abnormality. The lower pole of the right kidney was palpable. Pelvic examination did not reveal any abnormal findings. Fluoroscopy showed no abnormality in the chest. The urine did not contain any albumin or sugar.

With the tentative diagnosis of a chromaffin tumor, the patient was hospitalized for a few days in the Glendale Sanitarium, in order to study her during the attacks.

In the hospital several attacks were observed by the house physicians and nurses. During one attack the blood pressure rose from 120/80 to 230/40. Concurrently, a sudden rise in blood sugar was noted. During an attack June 5 at 11:30 A.M., the blood sugar was found to be 245 mg. per 100 cc. of blood, whereas the fasting blood sugar was 98 mg. per 100 cc. of blood. During another spell June 7, the blood sugar was found to be 150 mg. at 12:15 P.M., 160 mg. at 12:30 P.M., and 148 mg. at 12:45 P.M. During the attacks a marked swelling of the neck was noted in the region of the thyroid gland.

The patient was advised to have an x-ray study, with air insufflation in the area of the adrenals, and to undergo surgical treatment for the supposed chromaffin tumor. She requested, however, that a final effort be made to treat the condition medically. Although no hope of successful medication was held out by us, she was placed on pro-

stigmine bromide. Prostigmine was suggested because of its parasympathetic stimulating action, which conceivably might have counteracted the sympathetic stimulation experienced by the patient during an attack. However, oral administration of 15 mg. of prostigmine bromide three or four times each day produced no apparent improvement. The spells became more and more frequent, and August 18, one of us, Bauer, observed the patient during a typical attack. The course of the attack proceeded as follows:

The patient entered Dr. Bauer's office at 11:05 A.M., announcing the sudden onset of an attack. She felt extremely tired and weak; her heart was pounding; her arms, legs, back, and neck ached and pained; she felt a swelling of her neck; she was nauseated and shaking. The patient's face was pale; her hands showed a fine tremor; her thyroid was markedly enlarged, its contours being clearly visible. The whole gland was bulging; the skin over the frontal part of the neck was hyperemic; however, no thrill or bruit was found over the thyroid. The attack lasted approximately twenty minutes. The patient's fingertips and fingernails were slightly cyanotic at the end of the attack. The swelling of the thyroid disappeared completely in a few hours. The pulse rate at the onset of the attack was 84 and rose in 10 minutes to 96; the blood pressure was found to be 210/60 at 11:10 A.M. (five minutes after onset). It was taken at two to three minute intervals, and showed the following extreme variations during the next twenty minutes: 130/60, 240/75, 190/70, 100/60, 154/85, 100/70, 110/80. The blood pressure did not vary after 11:32 A.M. when the patient declared her attack was over. The pulse then was 80.

The patient now consented to an operation and she was seen August 10, 1945 by Dr. Belt. Urologic examination revealed the following:

An x-ray of the genito-urinary tract showed the kidney shadows to be normal in size, shape and position. A large round gallstone, the size of a quarter, appeared in the region of the gallbladder. The liver was normal in size. The iliopsoas shadows were clearly seen. By x-ray no mass was seen in either adrenal area. A number twenty-four cystoscope entered the bladder readily. Visual examination of the bladder revealed a normal mucosa. Both ureteral orifices were seen clearly, both functioned normally, and both were catheterized. Specimens from both kidneys were collected for Gram's stain and culture. Neither pus nor stainable bacteria were seen in either specimen of kidney urine; on culture both revealed gram-positive cocci. Retrograde pyelograms revealed a normal kidney pelvis on the left, with normal calices and a normal ureter pursuing a normal course to the bladder.

In the standing position the left kidney did not descend materially. It emptied promptly into the bladder. On the right side there was a hydronephrosis, Grade I, on the basis of I to IV. The ureteropelvic juncture showed an obstruction approximately 3 cm. below the renal hilus. From this point upward the ureter was somewhat dilated, a dilatation which extended to the renal calices. In the standing position this kidney descended a distance of 2 to 2½ cm., and in descending caused the ureter to kink 3 cm. below the right ureteropelvic juncture. In the retrograde pyelograms, displacement of the right kidney was very marked; it occurred only when the patient was in an upright position. In the roentgenograms taken without air insufflation around the adrenals, no definite evidence of an adrenal tumor could be discerned on either side.

The patient returned to the office August 18 for further study. At this time 60 cc. of air was injected into the perirenal space posterior to the kidney on each side. Diodrast was administered intravenously to bring out the shadows of the kidney parenchyma. A series of x-ray pictures was taken, first in the horizontal and then in the vertical position, in order to demonstrate the adrenal area. The left adrenal area was sharply defined and appeared to be normal. The right adrenal area was also clearly demarcated. At the

upper pole of the right kidney, extending upward toward the diaphragm, a tumor mass was seen which was the size of a golf ball. This growth was seen to move with the kidney and was interpreted as a right adrenal tumor.

Treatment: The tumor was surgically removed August 31, 1945. Under spinal anesthesia, the patient was placed in the overhand-swimming position with the right side up. An incision through the skin was made between the last two ribs. The periosteum of each rib in turn was exposed. It was incised along the middle of the outer aspect of the rib, and each rib was lifted out of its periosteal bed. The pleura was elevated carefully, the crus of the diaphragm was retracted upward, and a round, tense, cystic adrenal mass was exposed. It was covered with a network of distended veins. The vessels of the pedicle were ligated one after another, and just as the base was reached the cystic mass suddenly ruptured. Its content of brownish fluid, glistening with crystalline flakes of hemosiderin, filled the wound and was picked up with a sponge. The shell of active pheochrome tissue was then lifted easily from its bed. Complete hemostatis was assured and the wound was closed, leaving in place only one small rubber drain. During the period of operation no hypertensive crisis occurred. The patient made an uneventful recovery, was up on the third postoperative day, and left the hospital on the tenth postoperative day. She had no further attacks, although for a time the pulse and blood pressure showed moderate variations, both spontaneous and provoked by changes in posture. These variations were not associated with any discomfort and gradually subsided. Subsequently, October 9 and 16 respectively, the following pulse rates and blood pressures were recorded:

	Recumbent	Sitting	Standing
Pulse	80	84	96
B.P.	150/90	140/90	140/95–130/100
Pulse	68	72	80
B.P.	145/90	130/80	130/100

The tumor tissue removed at surgery was examined by Dr. Reuben Straus, pathologist of the Cedars of Lebanon Hospital. He reported as follows:

"*Gross description:* The specimen consists of a newly opened cystic structure measuring approximately 6×6×5.5 cm. in diameters. It weighs 31.3 gm. The external surface is roughened in several areas by fibrous bands, and further presents several portions of bright yellow tissue having the color of adrenal cortex. This is present on two aspects of the mass, and is generally flattened. It appears compressed, so that only small ribbons of tissue traverse the external surface of the mass. The external surface is gray in color and presents a few areas of hyperemia. The wall of the cystic structure varies in thickness from about 2 mm. to a maximum of 11 mm. The maximum thickness is reached in the area of a smooth, rounded eminence, which projects into the cystic cavity. This eminence measures 3×3 cm. in transverse diameters. On section this eminence presents a pale, glistening, homogeneous, apparently cellular surface, the appearance of which is not unlike that of a lymphosarcoma. The lining of the cyst, which generally is not smooth but glistening, is pale tan, although areas of dark brown discoloration are seen.

"*Microscopic description from seven sections, suprarenal gland:* Six irregular pieces show portions of a cystic tumor mass. The inner surface of the cyst has no characteristic lining. Slight hemorrhage is noted here. The tumor is composed of large, irregular, poly-

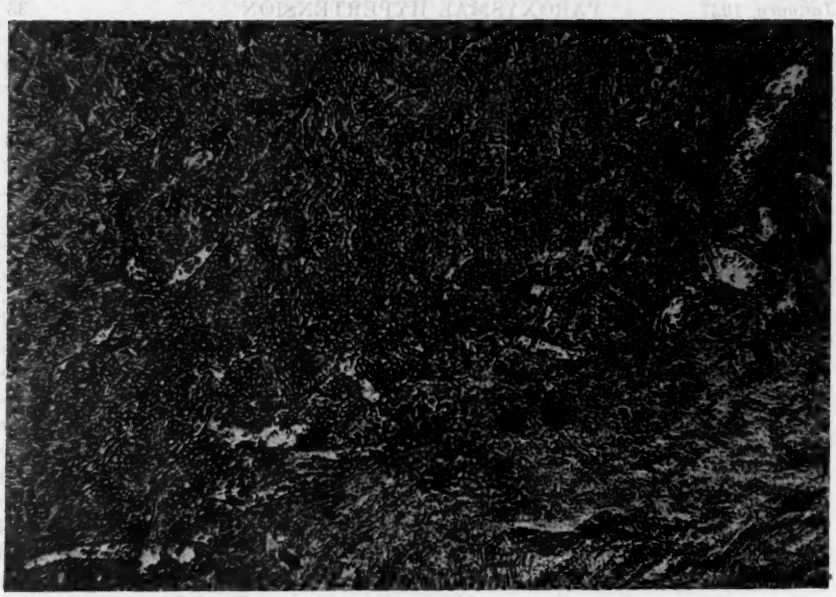

FIG. 1. Low power view (×100) of margin of tumor.

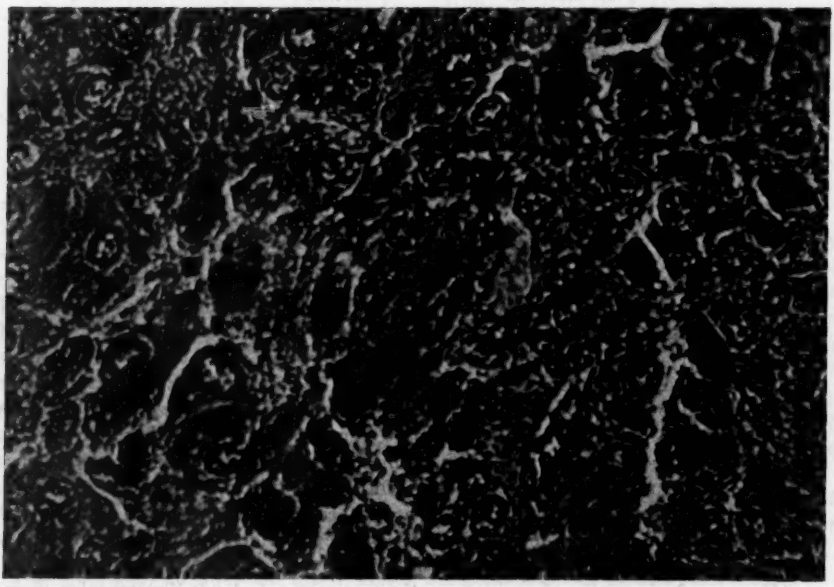

FIG. 2. High power view (×450) of tumor cells. Dark brown granularity in the cytoplasm of some of the tumor cells.

hedral cells. The cytoplasm is abundant and lavender stained. The nuclei are small, fairly uniform, and some are hyperchromatic. The tumor is well vascularized. The external surface is bordered by a thick fibrous capsule. One of the pieces of tumor has a small amount of suprarenal cortical tissue, showing to a large degree compression atrophy and replacement fibrosis. Additional sections of the tumor, fixed in Zenker, Helly and Zenker's acetic acid, show a diffuse brown discoloration of all the tumor cells. Certain of the cells, however, show a distinctly darker brown granularity of the cytoplasm. Penetration of the tumor by the bichromate is somewhat uneven.

"*Diagnosis:* Cystic pheochromocytoma of the suprarenal gland."

DISCUSSION

Several problems arise in hazarding a diagnosis of chromaffin tumor. We shall discuss a few of these in some detail, with a brief note on the treatment, pathogenesis, and pathology of the tumor itself.

Diagnosis: In our case the tentative diagnosis of a chromaffin tumor was based on the patient's description of her typical attacks, and on the fact that these attacks were associated with paroxysmal arterial hypertension. It was corroborated by the finding that paroxysmal hyperglycemia accompanied the attacks. Hence, the adrenalogenic nature of the disease was almost assured, since the attacks simulated entirely the effect of an intravenous administration of adrenalin (epinephrine). The diagnosis was established when the supposed tumor was visualized in the x-ray plate by perirenal insufflation.

Paroxysmal arterial hypertension is not necessarily indicative of the presence of a chromaffin tumor. Two monographs exist on paroxysmal hypertensive crises, the first published in 1905 by Pal (35) of Vienna, the second in 1934 in Paris by Bernal (8). Such crises have been observed in eclampsia, lead poisoning, essential hypertension, nephritis, aortitis, and various diseases of the nervous system such as epilepsy, traumatic or vascular damage to the brain, or meningitis. In a case of subacute meningococcic meningitis reported by Weber (45), paroxysmal elevations of systolic blood pressure from 130 to 240 were observed. In a case of tabes, studied by Rowntree and Ball (40), paroxysmal elevations of systolic blood pressure from 90 to 235 occurred. The supposed adrenal tumor was found neither at operation nor at autopsy. Hypertensive crises may accompany a diseased gasserian ganglion, Trémolières and Véran (42), a sciatic neuritis, or a compression of the vagus by tumor masses, Donzelot (20) and Villaret (44). Vascular hypertensive crises have been reported in rare cases of typhoid fever and other acute infectious diseases. Monier-Vinard (31) observed paroxysmal hypertension caused by an allergy to Madeira wine. A patient reacted regularly to a glass of Madeira wine with a paroxysmal rise of his blood pressure from 160/90 to 280/140. This allergic reaction was provoked many times during a long period of observation.

These different varieties of paroxysmal hypertensive crises are probably brought about by a direct central or reflex stimulation of the medullary vasomotor center. This may, or may not, involve excessive liberation of epinephrine by central irritation of the splanchnic nerves. In a hypertensive crisis, if the diastolic pressure is only slightly elevated or not elevated at all, or if it drops even below the original level, then we are justified in presuming that the effect is due to the action of epinephrine. It was shown in 1912 by one of us, Bauer (2), that epinephrine, administered subcutaneously, may lower the diastolic pressure. Occasionally it may lower the pulse rate, probably by central stimulation of the vagus.

Paroxysmal hyperglycemia may or may not accompany paroxysmal hypertensive crises. Bauer and Leriche (4, 5) first reported a case of chromaffin tumor in which paroxysmal hyperglycemia accompanied the hypertensive crises. During an attack the blood sugar rose to 235 mg. % and fell to the usual value of 96 mg. % after 2½ hours. Van Epps, Hyndman and Greene (43) reported a case in which the blood sugar rose from 110 to 273 mg. % during the hypertensive crises. This sign, however, is variable. It was absent in a second case of Van Epps, et al., as well as in a patient examined by Engel, Mencher and Engel (22). A patient of Mortell and Whittle (32) showed a rise of his blood sugar from 100 mg. % to 245 mg. % during a hypertensive spell. Cahill (13) mentions a decrease in blood sugar during an attack, "evidently from rapid use of blood glucose." He does not cite a particular case or give figures. This action certainly is not in accord with the known effects of hyperadrenalinemia, nor does it conform with the mild transitory glycosuria observed in some cases after a hypertensive crisis. Paroxysmal hyperglycemia and transitory glycosuria, accompanying hypertensive crises, are not confined to chromaffin tumors, but may occur in other diseases. Therefore, paroxysmal hyperglycemia alone does not prove the presence of a chromaffin tumor.

Provocation of hypertensive attacks by any mechanism which calls forth an adrenalin discharge may be suggestive of the presence of a chromaffin tumor. Hyman and Mencher (26) enumerate the following causative factors of hypertensive attacks: emotional upsets, fear, anger, slight trauma, change in posture, massage on the side of the tumor, administration of histamine Roth and Kvale (39), or adrenalin, or immersion of the extremities in cold water. Artificial provocation of an attack did not occur in our case or that of Bauer and Leriche (4, 5). In the case of Belt and Powell (7), however, the tumor mass must have been compressed when they placed the patient on the surgical table in the overhand-swimming position and raised the kidney lift, thus provoking an attack of hypertension which terminated in death.

Demonstration of adrenalin, or at least of a pressor substance in the

blood of a patient during a hypertensive crisis, also may be suggestive of the presence of a chromaffin tumor. By chemical analysis Ernould and Picard (24) found increased adrenalin in the blood of such a patient. Beer, King and Prinzmetal (6) demonstrated the presence, during a hypertensive crisis, of a pressor substance in the blood of a patient with a chromaffin tumor. They used a modification of Pissemki's (37) method (perfusion of the denervated rabbit's ear). Since in their experiment the pressor effect of the blood was suppressed by ergotamine tartrate, it is almost certain that during the hypertensive crisis adrenalin was circulating in the blood in excessive amounts. In a case reported by Hyman and Mencher (26), (case 3), a pressor effect of the patient's blood during a hypertensive crisis was demonstrated on a dog's tail preparation; and an adrenalin-like effect was also obtained on a denervated cat's eye. A less delicate method of detecting adrenalin, by perfusion of a frog's leg, failed to give a positive result in the case of Bauer and Leriche (4, 5).

Demonstration of a vasopressor substance in the blood of a patient during a hypertensive crisis, however, is not necessarily indicative of the presence of a chromaffin tumor. Brandt and Katz (11) found such a pressor substance in the blood during hypertensive crises in a number of cases of paroxysmal hypertension due to causes other than chromaffin tumors. The following pharmacodynamic tests were employed, indicating that the pressor substance was actually adrenalin: (1) Pissemski's (37) method of perfusion of a rabbit's ear, (2) registration of the movements of an isolated rabbit's intestines, and (3) the mydriatic effect on an isolated frog's eye. All of these tests indicated that the pressor substance actually was adrenalin, the effects of which were abolished by ergotamine tartrate. Bernal (8) transfused into a normal person 300 cc. of blood which was withdrawn from a patient while suffering from an attack of paroxysmal hypertension. He observed a pressor effect of the transfused blood, which did not occur when blood was taken from the same patient during a free interval or from other patients not suffering with paroxysmal hypertension. The patient, whose blood exerted a pressor effect during the hypertensive crisis was not, however, suffering from a chromaffin tumor but from chronic lead poisoning. Demole and Rutishauser (19) report an extraordinary case of paroxysmal hypertension occurring in a patient suffering from a tuberculous destruction of the left adrenal gland only. The systolic blood pressure rose during the crises from 140–170 mm. Hg. to 210–250 mm. Hg. At the same time the blood sugar rose from 91–100 mg. % to as high as 170 mg. %. Transfusion into a normal recipient, of the blood taken from this patient during a hypertensive crisis, markedly raised the recipient's blood pressure and blood sugar for a period of ten minutes. This reaction failed to occur if other blood was used for transfusion.

We conclude, therefore, that demonstration of an adrenalin-like pressor substance in the blood of patients during hypertensive crises may be an interesting corroboration of the diagnosis of a chromaffin tumor, but is nonspecific and, therefore, not diagnostic of the presence of a chromaffin tumor. For practical diagnostic purposes it may be omitted.

Visualization of the tumor on the x-ray plate is the most important diagnostic procedure in cases of chromaffin tumors. In some cases pyelography may show a displacement of the kidney by such a tumor, Belt and Powell (7). Perirenal insufflation introduced by Carelli (16, 17, 18) in 1921, and popularized in this country particularly by Cahill (14, 15), will in most cases enable us to ascertain the diagnosis, and at the same time permit the surgeon to proceed with assurance to extirpation of the tumor. If x-ray studies do not support the tentative diagnosis of a chromaffin tumor, however, the clinical diagnosis may nevertheless be correct. A small adrenal tumor, or one that lies outside the adrenal gland, i.e., a paraganglioma, may escape visualization in the x-ray even with the aid of perirenal air insufflation. In the case of Bauer and Leriche (5) for instance, the cherry-sized paraganglioma adjacent to the left adrenal gland probably would not have been seen even after perirenal air insufflation. Such paragangliomas may be located even in the thoracic cavity, Phillips (36), in which position they certainly would not be visualized in the x-ray picture.

X-ray study after perirenal air insufflation is therefore, an indispensable diagnostic procedure, but a negative result does not disprove the presence of a chromaffin tumor.

Extremely rapid and excessive variations in the blood pressure were recorded during a hypertensive paroxysm in the patient here presented. To our knowledge such an observation has been made only once hitherto. We saw the blood pressure shifting, within a few minutes, from 210/60 to 130/60, then again up to 240/75 and down to 100/60. Mortell and Whittle (32) noted shifting of blood pressure in five minutes from 300/180 to 160 systolic, returning again in the next five minutes to 300 systolic. It is hardly possible to decide whether the excessive output of adrenalin took place in intermittent pushes, or whether the blood pressure variations were due to rapid changes in the responsive threshold of the vasoconstrictors. In Engel, Mencher and Engel's (22) case also, there were striking variations in the blood pressure; however, they were not as rapid as they were in our patient, nor did they occur during one hypertensive attack. Following a severe hypertensive crisis of unusual length, their patient showed a serious fall in blood pressure to 76/60, a level which persisted for several hours. Since the fall was associated with hemoconcentration, tachycardia, and torpor, the authors suggest "epinephrine shock" as a manifestation of pheochromocytoma of the adrenal gland. They compare this effect with that following the

prolonged administration of large doses of adrenalin in animal experiments. In 1918 it was shown, by Bauer and Froehlich (3), that prolonged perfusion of a frog's leg with adrenalin in weak concentrations inverts the vasoconstrictor effect of various short stimuli into a vasodilator effect. Faradic stimulation of the lumbosacral plexus, adrenalin in high concentration, pituitrin, and strychnine were the stimuli used in the experiment. A similar mechanism may be operating to produce the extreme variations in blood pressure as noted in some patients with chromaffin tumors. Engel and Aring (23) observed tremendous variations in blood pressure in an 18 year old patient with a cyst in the thalamus. The blood pressure was once found to be 88/40, and a few hours later 180/130. Less than a year before death it was 220/160, and the next day 120/80.

The abnormal carbohydrate metabolism noted in some cases of chromaffin tumor may be the result of an inadequate adjustment between the adrenalin output and the requirements of the body. The glucose tolerance test on the patient reported by Beer, et al. (6), and by Hyman and Mencher (26), revealed extreme variations in blood sugar which rose from 65 mg. % to 240 mg. % in one hour, followed by a fall to 50 mg. % at the end of three hours. The fasting blood sugar of the same patient fell from 105 mg. % to 15 mg. % one and one-half hours after the injection of 10 units of insulin, the fall being accompanied by profound hypoglycemic shock. A patient reported by McCullagh and Engel (29) showed similar unusual blood sugar variations in a glucose tolerance test, fluctuation extremes being from 128 mg. % to 267 mg. %, then down to 45 mg. %. In the case of Mortell and Whittle (32) the glucose tolerance test showed a shifting from 163 to 253 mg. %, and in three hours, to 74 mg. %. In a remarkable case of pheochromocytoma observed by Thorne, Hindle and Sandmeyer (41), the glucose tolerance test following administration of 100 gm. glucose revealed a paradoxical result: the fasting blood sugar was 130 mg. %; after thirty minutes the level was 100 mg. %; after one hour it was 68 mg. %; after two hours it was 77 mg. %; and after three hours it was 85 mg. %. The authors do not comment on this very strange result. This case, incidentally, showed persistent hypertension, rather than paroxysmal hypertension, and was cured by surgical removal of the tumor.

Paroxysmal diffuse swelling of the thyroid, accompanying a hypertensive crisis, is an extraordinary feature in our case which, to our knowledge, has not been reported in the literature. It was obviously caused by an intense paroxysmal hyperemia of the thyroid gland. The close relationship known to exist between the thyroid gland and the adrenal medulla was emphasized by Belt and Powell (7) in the study of the reaction of pheochrome tumors upon the thyroid gland, as revealed in many of the cases presented in the literature. One can only speculate about the mechanism

of this unusual sign which occurred in our patient. It might be explained on the basis of some facts outlined by the physiologist, Rein (38), and his coworkers. These investigators found that the carotid sinus nerve exerts a permanent depressing action upon the vasomotor tonus of the thyroid vessels. Severing of the nerve leads to a diminished blood flow through the thyroid, even without an essential alteration in the blood pressure.

Electric stimulation of the nerve, as well as a sudden increase in pressure in the carotid sinus, however, results in a considerable increase in blood flow through the thyroid gland. Therefore, the sudden rise of blood pressure in the carotid sinus, during the hypertensive crises in our patient, may have caused the tremendous transitory hyperemia of the thyroid with consequent enlargement of the gland. The reason this sign never has been reported in other cases with the same disease may be due to two factors: (1) it may have escaped the attention of both the patient and physician, if it occurred only in a mild degree, or (2) it may have occurred only in certain persons in whom the carotid sinus nerve was particularly sensitive. It was emphasized by Bauer (2) in 1912 that individuals vary in their reaction to the administration of adrenalin.

The pathogenesis of the paroxysmal crises in chromaffin tumors is a matter of conjecture. It is an established fact that these tumors always contain excessive amounts of adrenalin, the release of which obviously must be responsible for the crises. Hypertension, therefore, is a problem of the outpouring of adrenalin rather than its manufacture. Mechanical irritation of the tumor by changes in posture or other factors is not a satisfactory explanation of periodic hypertension. Emotional excitement does not regularly precede the hypertensive crisis; nevertheless, it is evident that the physiologic mechanism which normally regulates the discharge of adrenalin is dramatically modified in these patients. The mechanism responsible for this change is undoubtedly nervous in origin, i.e., sympathetic impulses reaching the chromaffin tissue by way of the splanchnic nerves. Bauer (1) pointed out elsewhere that frequently we meet with hormonal disorders which result from changes in the mechanism of discharge rather than from changes in the production of the particular hormone. Thus a vicious circle is established by the excessive amount of adrenalin released by the chromaffin tumor, which acts as a powerful excitant to the sympathetic system. In turn, the parasympathetic system is stimulated with consequent nervous and hormonal (insulin) counteractions. Finally, the entire autonomic nervous control of the body is upset, resulting in the ultimate discharge of insulin which counteracts the adrenalin. Individual constitutional differences, in the response of the various organs involved, may explain the differing clinical pictures resulting from the action of chromaffin tumors.

Not all cases of chromaffin tumor present the classical picture of paroxysmal hypertension as we saw it in our patient. Some develop a more or less rapidly progressive, permanent arterial hypertension, resembling the "essential" variety of hypertension. According to Nuzum and Dalton (34), an analysis of the cases reported revealed that the paroxysmal type of hypertension occurred in 22 cases; the constant type in 19. In rare cases of pheochromocytoma permanent hyperglycemia and glycosuria are displayed, instead of paroxysmal hyperglycemia and glycosuria. Clinically, these closely resemble the usual variety of diabetes and may be associated with it, Biebl and Wichels (9); McCullagh and Engel (29). However, in these cases of hyperglycemia and glycosuria associated with an adrenal medullary tumor, the syndrome is relieved by removal of the chromaffin tumor, Duncan, Semans and Howard (21). These cases represent one variety of what Bauer (1) named "symptomatic" hypertension and diabetes mellitus, as contrasted with the far more frequent, constitutional (genetic) types of these diseases. In the first instance, hypertension and diabetes mellitus are but symptoms of the presence of the chromaffin tumor; in the second instance, they are disease entities as such.

In certain cases of pheochromocytoma, unusual spontaneous variations in blood pressure occurred which were not followed by the characteristic clinical manifestations. In cases associated with diabetes mellitus, extremely variable spontaneous blood sugar levels have been recorded, McCullagh and Engel (29). Spells of nervousness, weakness and profuse perspiration may occur, which are not associated with or caused by paroxysmal hypertension or by paroxysmal alterations in the blood sugar level, McCullagh and Engel (29). The basal metabolic rate may be elevated and may mislead the observer into making an erroneous diagnosis of hyperthyroidism. The imbalance of the autonomic nervous system, created by the excessive production of adrenalin and more specifically the dramatic discharge of this hormone, may result in quite different clinical pictures, depending on individual variations in the response of the effector organs.

The pathology of chromaffin tumors has been described by Belt and Powell (7), and more recently by Nettleship (33). It requires no further comment here. The cystic type of pheochromocytoma found in our case is infrequently reported in the literature. The sharply defined, smoothly rounded contours of the tumor, as shown in the x-ray plate, suggest a cystic pheochromocytoma. The cyst form is caused by necrosis of the central part of the large tumor.

There was no indication of malignancy in our patient. Malignant pheochromocytomas are rare. Up to 1942, McGavack, Benjamin, Speer and Klotz (30) collected from the literature only eight reports of malignant pheochromocytomas. These metastasizing malignant tumors do not pro-

duce paroxysmal hypertension, and the term "pheochromoblastoma" probably would be more appropriate for them, Belt and Powell (7).

Occasionally pheochromocytomas may develop in two or more sites of chromaffin tissue, McCullagh and Engel (29), either simultaneously or successively. Therefore, removal of a single growth, when two or more exist, may explain failure in obtaining cure or relief of the symptoms in cases of dual tumors. Multiple sites of the pheochrome tumor also may account for recurrence of the disease at a later date, MacKenzie (28).

Constitutional predisposition to pheochromocytomas has to be assumed on the simple grounds that very few persons become victims of this disease and no extrinsic etiologic factors now known are responsible for its development. This is but a special instance of the problem of constitutional predisposition in the formation of tumors in general, and of tumors of endocrine glands in particular. In the etiology of tumors, Bauer (1) suggests two predisposing factors: (1) a general neoplastic tendency, and (2) a local factor.

The best illustration of the constitutional (genetic) background of pheochromocytomas is presented in the paper of Hyman and Mencher (26). They report such tumors, successfully proven by surgery, in two members of the same family, an aunt and her niece. Furthermore, an older sister of the aunt died at the age of 28 years with a clinical picture strikingly suggestive of that presented by the patient herself. According to the hospital record this was believed to be a rare disturbance of the sympathetic system. The constitutional "weak spot" in this family was not limited to the chromaffin system, but involved also the thyroid. The first patient with pheochromocytoma, the aunt, had been thyroidectomized as a young girl. A microscopic diagnosis of adenocarcinoma of the thyroid gland was made and confirmed by expert pathologists. The patient's mother and two sisters also had thyroidectomies. Her niece, the second proven case of pheochromocytoma in the family, also had a moderately and diffusely enlarged thyroid.

In our case, familial diabetes indicates the presence of a genetic biologic inferiority of the endocrine system in particular, secondarily involving the chromaffin tissue. The late onset of menarche in our patient may also be mentioned as a constitutional endocrine stigma.

Treatment: It was already clear by 1934, Belt and Powell (7), and Bauer and Leriche (4, 5), that when surgical removal of the pheochrome tumor was successful, it completely relieved the patient of all signs and symptoms typical of the suprarenal sympathetic syndrome. Hence, surgical extirpation, where possible, is the treatment of choice. The surgical approach is more readily planned if the site of the tumor has previously been demonstrated by the perirenal air insufflation technic, as it was in the case here

presented. Exposure of the adrenal is not difficult when properly planned.

Spinal anesthesia is selected because of the complete relaxation it affords. The position is of utmost importance. The patient is placed in the overhand-swimming position with the tumor side up. The upper leg is outstretched, the lower leg flexed at the knee. A lift, just below the last rib of the opposite side, is raised to a degree of elevation sufficient to extend the space on the upper side, between the iliac crest and the last rib, to its greatest extent. The patient should be rolled forward slightly on the abdomen to permit the extension of the incision backward to the angle of the ribs and spine. The skin incision is made along the lower border of the eleventh rib. It is carried through the muscles overlying the eleventh rib to the periosteum of the rib itself. Both the eleventh and twelfth ribs are removed throughout their entire length leaving the periosteum of each. The eleventh and twelfth intercostal nerves are depressed, and the wound is extended forward by bluntly spreading the abdominal muscles. The peritoneum is pressed medially, beginning in the most inferior angle of the wound, and the pleura is carefully deflected upward. The adrenal is thus easily revealed. Its blood vessels are numerous; each in turn is doubly ligated and cut between ligatures until the adrenal and its tumor is thus completely freed of all attachments. The gland is then lifted from the wound.

In the preoperative preparation it seems wise, from the experiences reported by Biskind, Meyer and Beadner (10), to place the patient on a high salt intake and give desoxycorticosterone acetate intramuscularly. Postoperatively, if the blood pressure falls or remains low, epinephrine may be given intravenously and subcutaneously with adrenocortical extract, as well as whole blood in transfusions, and intravenous fluid, also carrying epinephrin, in continuous intravenous drip. In the case here reported, a well-developed left adrenal was demonstrated in the preoperative air insufflation roentgenogram; therefore, adrenal insufficiency was not expected nor encountered. Extraordinary measures of preoperative preparation and postoperative care did not prove to be necessary. There was no operative or postoperative shock.

Conclusions: A disturbance in the adrenal gland, due to a pheochromocytoma, may cause swelling of the thyroid as a result of the spread of sympathetic stimuli during an attack of paroxysmal hypertension.

Surgical intervention, with the removal of the tumor, is necessary to effect a relief from this bizarre syndrome.

SUMMARY

A case report is presented in which, added to the usual signs and symptoms characteristic of the suprarenal sympathetic syndrome, a sudden

swelling of the thyroid gland was observed. This swelling reached its peak, and faded away, concurrently with the rise and fall of blood pressure, in each hypertensive attack.

A cure of this feature and of the entire suprarenal sympathetic syndrome was effected by the surgical removal of the pheochrome tumor.

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THE EFFECT OF THIOURACIL DERIVATIVES ON FETUSES AND INFANTS

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GRADUALLY, as derivatives of thiouracil become of general use in the treatment of hyperthyroidism, it proves necessary to find out whether cretinism in a light or severe degree can be induced in the fetus by administration to the mother's organism of an antithyroid substance.

Clinical experiences in this problem are scarce. Eaton (3) reported two cases in which thiouracil was given to pregnant women suffering from hyperthyroidism. One of these women bore a child whose thyroid was transitorily enlarged for some time after birth. The child was normal in all other respects. In the case of the other woman the thiouracil treatment was discontinued four weeks before parturition. This woman likewise bore a normal child. Palmer (7) treated with thiouracil three pregnant women suffering from hyperthyroidism. In one case the treatment was continued from the fourth to the ninth month; in other words, right up to parturition. The child was normal in every respect.

In the Bispebjerg Hospital, Medical Department B, a 36 year old woman was treated successfully for hyperthyroidism, through the first period of her pregnancy, with adequate doses of methylthiouracil. Because of complicating heart failure the fetus was removed in the fifth month of pregnancy. The thyroid gland of the fetus, which had a total length of 23 cm., was hyperplastic, weighing 335 mg. The average weight of the thyroids of ten normal controls of corresponding size varied from 150 to 260 mg.

Vogt (8) reported a 25 year old pregnant woman suffering from hyperthyroidism. She was treated with methylthiouracil, 600–100 mg. per day, until parturition. Although she herself developed a marked goiter during the treatment, there was no thyroid enlargement in her child.

The effect of thiouracil on pregnant rats and on the growth rate of immature rats has been described in detail by Hughes (4). Hughes induced a pronounced myxedema in infantile rats by administration of thiouracil from the first day of life. The cretinism manifested itself by retardation of growth and development of bones, a mild degree of anemia, great mortality, and development of thyroid hyperplasia. "The young of thiouracil-treated mothers appeared to be normal but showed evidence of thyroid hyperplasia as early as one day of age, and retarded development at ten

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days, indicating the possibility of placental and mammary transmission of the drug. Cretinism was not seen if thyroxin was given concurrently." Even feeding thiouracil to hens may cause thyroid enlargement in chicks, Andrews and Schnitzler (1).

The question which must be of particular interest to the clinician is whether the thiouracil effect can injure the fetus in the uterus. Hughes' (4) experiments seem to show that the growing organism is very susceptible to a deficiency in thyroid hormone. As the thyroid hormone is generally supposed to be able to pass through the placenta from mother to fetus, the latter need not necessarily be subject to thyroxin deficiency even if it is exposed to thiouracil from the mother. In the treatment of hyperthyroidism, the dose of thiouracil is generally adapted to preserve an approximately normal thyroxin concentration.

During the treatment of hyperthyroidism in human pregnancy the fetus may be influenced by thiouracil if this substance really passes through the placental membrane. The extent to which the blocking of thyroxin production may be compensated for is dependent upon the super-normal production of thyroxin by the mother and the fetus itself.

As this problem could not be studied systemically in women, because of the possible consequences to the fetuses, we have studied the development of the fetuses and the young of rats and rabbits during the influence of 4-methyl-2-thiouracil administered directly, through the diet, or indirectly, transplacentally or transmammarily, by administration to the mothers. The details will be published in *Acta Pharmacologica et Toxicologica*, 1946.

RESULTS

Transplacental transmission of thiouracil derivatives. The following experiment was carried out with the object of proving that thiouracil compounds are transmitted transplacentally from mother to fetus. Some normal pregnant rats were fed on the usual standard diet +20 mg. 2-thio-4-n-propyluracil per 10 gm. diet, for four consecutive days. The uterus was opened and the fetus removed, great care being taken not to establish a contact between the blood or tissue fluid of the fetus and those of the mother. Each fetus, which was nearly full-grown, was washed thoroughly and next dried at 100°C. The fetus was then given to normal rats, mixed in the standard food. These rats developed typical thyroid hyperplasia. On the basis of our knowledge of thyroid hyperplasia after administration of propylthiouracil we could estimate the antithyroid effect of each rat fetus to correspond to 0.01–0.1 mg. propylthiouracil. Normal rat fetuses were found to contain no goitrogenic substances.

Effect of methylthiouracil *in utero*. In order to study the effect of methylthiouracil on the fetus, we fed a group of pregnant rats on a standard diet to which was added 0.25 mg. methylthiouracil per 10 gm. diet. This amount

of methylthiouracil suffices to bring about marked thyroid hyperplasia in less than ten days, and it parallels the dose used in human hyperthyroidism. Methylthiouracil was given from the time of conception to the day of parturition.

Several litters of normal rats which were fed on the same standard diet but with no addition of methylthiouracil served as a basis for comparison. The thyroids of all rat fetuses examined were found to consist of a solid cell mass with a little connective tissue. The more developed fetuses presented beginning differentiation into solid cell cords, but no colloid. (On this point the development of the human thyroid differs from that of the rat. Within the latter half of pregnancy the thyroid of the human fetus has a histologically more normal appearance with well-developed follicles.) After a few hours of life newborn normal rats presented a beginning development of colloid substance. The follicles increased quickly in number and size. In 10-day-old normal young the cell height was greater and the amount of colloid relatively smaller than in mature normal rats. Not until about the twentieth day of life did the thyroids of the young assume the same histological picture as that of a full-grown normal rat. These observations accord with Kull's (6) description of the late embryonic development of the thyroid gland of the albino rat.

The young which had received methylthiouracil transplacentally showed at birth signs of the results of a slight antithyroid effect, since the thyroid contained no colloid but consisted exclusively of solid cell masses. Colloid appeared in these cases one or two days later than normally, but the further development of the thyroid corresponded exactly to that of the control animals. No increase in weight of the thyroids of the infantile rats could be observed or registered. It should be borne in mind, however, that the thyroid of the normal, newborn rat weighs about 1 to 1.5 mg. Thus only slight transitory histologic changes could be demonstrated. The further development of these young was exactly like that of normal young. This was also the case with the young whose mothers had received a considerable amount of methylthiouracil in their diet, throughout pregnancy.

Transmammary administration of methylthiouracil. When methylthiouracil was administered to suckling rats immediately after parturition, thyroid hyperplasia could be traced in the young after one week, and twelve to fourteen days after birth a maximal thyroid hyperplasia was found. Such young presented a slightly retarded growth rate, expressive of an artificial, infantile myxedema, even though the addition of methylthiouracil to the mother's diet was discontinued before the end of the period of lactation, ten days after parturition. The period of lactation is supposed to last about twenty days or more. The thyroid was regenerated completely within less than one month.

Direct administration of methylthiouracil to young animals. A consider-

able retardation of growth, together with the development of an infantile myxedema, was observed in the cases in which the direct administration of methylthiouracil was continued after the period of lactation. These observations correspond exactly to Hughes' (4) descriptions.

Combined administration of methylthiouracil and thyroid hormone. The thyroid hyperplasia generally brought about by administration of methylthiouracil to infantile rats could be prevented entirely by concurrent administration of thyroid hormone. Thus it is plain that the dangerous element for the fetus and the growing organism is not the thiouracil as such, but the low concentration of thyroxin in the tissues induced by this substance.

DISCUSSION

The above experiments may illustrate to what extent the thiouracils are clinically applicable in pregnant and suckling women, and the information they give on the necessity of thyroid activity in fetal life is of physiologic interest. About the latter point there can be no doubt that the thiouracils can pass from the mother's organism into the fetus. Christensen (2) recently found that many of the antithyroid substances are highly protein bound when occurring in human plasma. Of 4-methyl-2-thiouracil and 4-n-propyl-2-thiouracil, only 35 and 8 per cent, respectively, were removable through ultrafiltration under corresponding circumstances. However, in our experiments this has not prevented sufficient amounts of the latter substance from penetrating the placental membrane. Considering the fact that the infantile growing rat is very susceptible to the influence of thiouracil, it is remarkable that the influence on the fetus seems to be rather small. This indicates that the thyroid hormone is not of vital importance for the course of the pregnancy and the intra-uterine development of the rat fetus. Attention should be called here to the fact that in the case of man the thyroid seems to function earlier in fetal life than in the case of rats. That the so-called congenital myxedema in man does not occur until a few months after birth, and that the thyroid of the fetus seems capable of reducing an existing myxedema in the mother, Zondek (10), are facts which argue greatly in favor of the theory that the thyroid hormone can pass through the placenta. Also the thyrotropic hormone is supposed to be able to pass through the placenta, Whiteside (9). When, therefore, a pregnant organism is exposed to the influence of a thiouracil derivative the fetus is hardly affected by the antithyroid substance as such, but the influence of this substance on the fetus probably depends on the effective amount of thyroid hormone present whether originating from the fetus itself or from the mother. Accordingly, when a pregnant woman suffering from hyperthyroidism is treated with a thiouracil derivative there should, theoretically, be no chance of injuring the fetus with the thiouracil as long as the

mother's metabolic rate is kept within normal values, but if the mother becomes affected during the treatment with an artificial myxedema, the fetus will share the same fate. For that same reason, overdosage during pregnancy is detrimental to the fetus. The use of thiouracil derivatives should be avoided entirely during lactation, because such drugs are so easily transmitted through the milk to the baby's organism, which is particularly susceptible to the antithyroid substances.

SUMMARY OF EXPERIMENTAL RESULTS

The experimental results obtained by Hughes (4), with 2-thiouracil, have been confirmed and extended through our experiments; 4-methyl-2-thiouracil administered directly to rats and rabbits could bring about pronounced cretinism in young animals or animals which received the substance through the milk.

Fetuses of pregnant rats which were given a diet containing 2-thio-4-n-propyluracil brought about thyroid hyperplasia in normal rats when the fetuses were mixed in the food of the latter. This was regarded as direct proof of the transplacental transmission of the thiouracil derivative from mother to fetus.

Rats which had been under the influence of methylthiouracil alone *in utero* showed evidence of only a transitory, slight thyroid hyperplasia, and no subsequent retardation of growth.

Administration of thyroid hormone concurrently with methylthiouracil prevented the development of infantile myxedema, as first described by Hughes (4). Thus it is not the thiouracil derivative but the thyroid deficiency that is detrimental to the quickly growing organism.

CONCLUSION

The probable conclusions of these results are that hyperthyroidism in pregnant women may be treated with thiouracils but overdosage should carefully be avoided; during lactation administration of thiouracils to the mother, or the lactation itself, should be discontinued.

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THYROID AND ADRENAL INTERRELATIONS WITH SPECIAL REFERENCE TO HYPOTRICHOSIS AXILLARIS IN THYROTOXICOSIS

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FOR SEVERAL decades many investigators have been interested in the interrelations of the thyroid and adrenal glands. With alteration in the function of one of these glands, physiologic and anatomic changes have been observed in the other. However, the many contradictory conclusions that have been drawn indicate the great need for elucidation. Although definite progress has been made in the last few years, there are many phases of the problem that are as obscure as is the etiology of Graves' disease.

Since it was noted, in the course of examining thyrotoxic patients, that many of them tended to have less axillary hair than normal, and since the amount of axillary hair is governed to a large extent by the androgenic function of the adrenals (1, 6), the interrelationship of the two glands was given further consideration. The results are reported in this paper. Our interest in the significance of axillary hair as an indicator of the androgenic function of the adrenal glands was aroused in 1941 by Dr. Fuller Albright. Since then it has been the policy of the author to observe carefully in all patients the amount of axillary hair regardless of what their main complaint may be. These observations represent the standards for comparisons in the thyrotoxic patients.

METHOD OF STUDY

Each of 102 thyrotoxic patients examined consecutively at the Boston City Hospital was included in the study. Without any preliminary explanation the patient was asked: "Do you have about the same amount of hair under your arms as does the average person?" If a subnormal amount of hair was observed, the patient was asked if it had always been less than normal, whether the amount had changed with the development of thyrotoxicosis, and whether any other members of the family had a subnormal amount of hair. When there was doubt as to whether there was a decrease in hair, the patient was credited as having a normal amount. The quantity of pubic hair was observed, but inasmuch as this hair is not as delicate as

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axillary hair as an indicator of decreased glandular function, most of the emphasis was placed on the changes in axillary hair. In determining whether the quantity of axillary hair present was normal, consideration was given to the sex, age and nationality of the patient, as well as other factors which might influence the amount of hair. In this connection, dam-

FIG. 1. Mother of several children, age 40, with moderate thyrotoxicosis; never had any axillary hair.

age of the liver was borne in mind, and in the last 70 of the 102 cases a record was made of the incidence of telangiectasia of the skin, liver palms, and gynecomastia.

RESULTS

Of the 102 patients examined, 50 (49 per cent) had a subnormal amount of axillary hair; nine either had no hair or a very rare sprig (Figure 1; Table 1). Sixty per cent of these patients had noticed that the amount of their axillary hair was moderately or markedly less than normal; 40 per cent had observed slight or no change. Twenty subjects were confident that they had always had a subnormal quantity of axillary hair. Twelve patients stated that the amount of axillary hair had decreased with the development of thyrotoxicosis, but one individual thought that there had

been an increase. Six patients were confident that the quantity of axillary hair was subnormal in from one to four members of their family.

Forty-three (86 per cent) of the patients with decreased hair were females; in the group with a normal amount of hair, 73 per cent were females. The patients with decreased hair were from 19 to 72 years of age, averaging 45 years; in the normal group the average was 36 years. The amount of hair was not related to the duration or the severity of the disease. No significant changes in the head or body hair were observed.

Of the 50 female and 20 male thyrotoxic patients who were examined especially for telangiectases, lesions of the spider type were found in 16 individuals, 14 of whom were females. These lesions consisted of very small

TABLE 1. AMOUNT OF DECREASE IN AXILLARY HAIR

	No. of Patients
+++++*	9
++++	8
+++	13
++	11
+	9

* +++++ = None or very few hairs present.
\+ = Slight decrease in amount of hair.

tortuous blood vessels which traversed each other, occasionally appearing to have a belly in the center. In some cases close inspection was necessary to locate the telangiectases. Simple linear dilations of the small vessels were not included because their significance is uncertain. Round, well-circumscribed, nodular telangiectases were noted to occur in 16 patients, but these were regarded as much less important than the spider-shaped ones. None of these vascular abnormalities was related to the age of the patient, the duration of the thyrotoxicosis, or to its severity. One individual, on becoming pregnant, experienced a great increase in the number of telangiectases.

Liver palms were noted in 16 subjects and gynecomastia in 3. One patient had hypotrichosis axillaris, gynecomastia, telangiectases of the skin, and liver palms. However, there was no clear-cut grouping of the disorders in the other cases. Some patients with very little axillary hair had no telangiectases, and the reverse situation was observed.

DISCUSSION

The quantity of axillary hair is subnormal in association with several diseases. It is decreased, ordinarily, in patients with Simmonds' disease, Addison's disease, hypogonadism, myxedema, or cirrhosis of the liver, and sometimes it is subnormal in other chronic debilitating diseases. Rarely

patients are seen who say that they have never had very much axillary hair although there is no evidence of any of the foregoing diseases. In some instances it is stated that there is a subnormal amount of axillary hair in most of the members of the family. This condition may be the result of a defect in the end-organ, i.e., the hair follicles, rather than the amount of hormone produced.

In considering the etiology of the hypotrichosis axillaris in our patients with hyperthyroidism, the presence of panhypopituitarism, Addison's disease, and hypogonadism can be disregarded. Although none of the patients had frank cirrhosis of the liver many of them may have had impairment of liver function. Weller (14) found, at necropsy, pronounced parenchymatous hepatitis in 22 of 44 cases of Graves' disease. Moreover, Youmans and Warfield (15) observed that impairment of liver function was common in this disease. In studying many cases of cirrhosis of the liver, decreased axillary hair was often noted (7). The not infrequent coexistence of telangiectases and liver palms, as well as decreased axillary hair, would be in accord with impairment of liver function. These changes, and the gynecomastia that was observed in three cases, could be associated with a decreased supply of androgenic hormone and a decreased inactivation of estrogens. Whereas the hypotrichosis axillaris possibly was related to impairment of liver function in some of the thyrotoxic patients, this would not seem to be the main pathogenesis, since in most instances the subnormal amount of hair was observed by the patient before the manifestations of hyperthyroidism appeared.

The question may be raised as to whether the subnormal amount of axillary hair signifies a decreased adrenal function, or some constitutional defect which predisposes to the development of thyrotoxicosis. In this connection, some of the work of Marine should be mentioned. In some patients developing Graves' disease, he regarded the constitutional background as one of the most important etiologic factors (8). He considered Graves' disease as ultimately associated with "insufficiency of some secretion of the suprarenal cortex and gonads." He stated that the changes in the thyroid represented a compensatory reaction to the abnormalities in the adrenals or gonads.

In the rabbit and cat with an intact thyroid, a transient symptom complex was produced by injury to the suprarenals, which was considered as closely resembling Graves' disease (9). The outstanding changes were increased metabolism beginning between the third and sixth day and lasting from a week to several months, myasthenia, regeneration of the thymus, hypertrophy of the lymph glands, increased appetite, increased irritability, and hypersusceptibility to drugs.

Shapiro and Marine (11) reported that in 50 cases of Graves' disease

feeding of a glycerol emulsion of very fresh ox suprarenal cortex caused a striking gain in body weight and muscle strength. On the other hand, Weinstein and Marlow (13), using an adrenal cortical extract of greater potency, did not find that the course of hyperthyroidism was influenced by this therapy. Crile (2) believed that the adrenals were hyperfunctioning in Graves' disease.

Hoskins (5) observed that desiccated thyroid produced hypertrophy of the adrenal cortex in young guinea pigs. Thyroxin does not induce adrenal cortical hypertrophy in the hypophysectomized animal.

Removal of the thyroid gland hastens atrophy of the thymus gland, while removal of the adrenal glands causes regeneration of the thymus. In thyrotoxicosis, many of the changes in lymphoid structure are the same as those in adrenal insufficiency. There tends to be enlargement of the thymus and spleen, and lymph nodes, and there is a relative lymphocytosis in the blood. Adrenotropin (3), or adrenal cortical extract, when administered to rats, causes a decrease in the size of the thymus, lymph nodes, and spleen, and a lymphopenia. Since Cushing's syndrome is a result of hyperadrenocorticism, some of the changes in this disease may be compared with some of those in thyrotoxicosis. Weakness is generally present in each, as is a decreased glucose tolerance test. Osteoporosis is rarely found in thyrotoxicosis, but often found in Cushing's syndrome. In the latter, there is usually an increased excretion of 11-oxysteroids (12), and 17-ketosteroids (4). In thyrotoxicosis there may be a decreased excretion of 17-ketosteroids in the urine (4). In thyrotoxicosis some of the adrenal changes probably are manifestations of a chronic alarm reaction, Selye (10).

SUMMARY AND CONCLUSIONS

A subnormal amount of axillary hair was observed in 50 of 102 patients 49 per cent, with thyrotoxicosis. In most of these cases the axillary hypotrichosis was apparently present before hyperthyroidism was manifested, and consequently the question is raised as to whether the decreased axillary hair is associated with some constitutional abnormality predisposing the individual to the development of thyrotoxicosis. The role of the adrenal glands and of the liver are given due consideration. Telangiectases of the skin and liver palms were not infrequently seen. The pathogenesis of these changes remains to be proven.

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Letters to the Editor

The following letters were received by the Editor concerning an article, *Is Endemic Goiter Due to a Lack of Iodine* by Dr. Isidor Greenwald, which appeared in the November, 1946, issue of this Journal.

TO THE EDITOR:

As secretary of the Committee for the Study of Endemic Goiter, a subcommittee of the American Public Health Association, I have received quite a few letters asking me about the article on endemic goiter appearing in the November, 1946, issue of *Clinical Endocrinology*. In January, I received a communication from Dr. Haven Emerson of the American Public Health Association. Another came from Dr. McClure, Chief Surgeon of Henry Ford Hospital, who has studied goiter in Detroit and Michigan for the past twenty years. Since then I have had numerous personal inquiries from men who could not understand the apparent contradiction. Also, this week I received reference to it which was published in *Science News Letter* and a clipping from the *New York Times* for February 23, 1947. These references suggest that someone is trying to bring this article to the fore as if it were the result of a thorough scientific study and nothing could be further from the truth than such a conclusion.

The article referred to is thirty-one pages with one hundred four references, without any data by the author himself showing basic clinical studies of goiter or studies on the prevention of goiter on a large scale either experimentally or in man. In the published letter from the former managing editor, Dr. K. W. Thompson, there is a paragraph in which Dr. Thompson refers to this paper as if it represented some basic scientific research with new findings.

The title of the paper is, *Is Endemic Goiter Due to a Lack of Iodine?* This immediately marks it as one dealing with the etiology of endemic goiter. On the very first page he jumps from the etiology of endemic goiter to the clinical findings in long-standing goiters which are two entirely different and unrelated conditions. The author says, "Before proceeding to a discussion of these mainstays of the 'iodine-lack' hypothesis, it seems desirable to examine three corollaries that follow from the proposition that "The immediate cause of the thyroid enlargement is a relative or an absolute deficiency of iodine,' or 'the immediate cause of

goiter is failure of the thyroid gland to obtain an adequate supply of iodine.' These are:

1. Goitrous individuals should have low metabolic rates.
2. Goiters should contain less iodine than do normal glands, not only per gram of tissue, but per entire gland.
3. It should be possible a) to produce goiter in animals by placing them on iodine-poor diets, and b) to prevent it by the addition to such diets of such small amounts of iodine as are found in ordinary foods.

None of these corollaries, with the possible exception of 3a is true."

To even think that the above statements which he calls corollaries should be true shows a complete lack of understanding of simple goiter. To try to draw such corollaries from the well-known teaching of Dr. David Marine, "The immediate cause of the thyroid enlargement is a relative or an absolute deficiency of iodine," is most fallacious. It is a well established fact that individuals with simple or endemic goiters may have perfectly normal metabolic rates. And, again, there is no truth in the statement that goiters should contain less iodine than normal thyroid glands. The iodine content can be anything from low normal to high concentration or all the iodine that can be stored in the thyroid. And for his third corollary it has been demonstrated by Dr. Marine and his associates that iodine-free diets will produce goiters and conversely that iodine will prevent hyperplasia or goiter formation. In a scientifically controlled study of the chemistry, physiology, and pathology of goiter there is no place at all for such loose phrases as iodine-poor diets or iodine as found in ordinary foods, and there is too much variation in the amount of iodine in foods and too great a variation in the excretion or re-metabolising of iodine by different animals to permit of a simple formula for the production of goiter. The amount of iodine per individual or animal, per health and disease and pregnancy and sex and age, can not be stated accurately in micrograms as the chemist, Von Fellenberg, thinks. Hence the larger amount of approximately one milligram per day, from iodized salt in this country, and judging from repeated study and rechecking over a period of twenty years in Michigan, this amount is efficient and entirely safe.

On page 732 Dr. Greenwald makes a reference to the studies I made in Cleveland in 1935. He takes just one figure of a comparative graph illustrating the data found in the survey in Cleveland which showed that in approximately 5,000 children who had used iodized salt continuously for years the percentage of goiter had decreased from 31% in 1924 to 7.7% in 1935. Instead of comparing this figure to similar groups in Cleveland which was given in the same graph, he compares this with a statement based on a survey made in Michigan where the decline was as great as I had given in

Cleveland, from 40% in 1924 to 8.2% in 1935. He emphasizes, however that the change in Michigan had been "regardless of whether or not iodized salt had been used." His inferences regarding the decline in the percent of goiter in Michigan are terribly wrong. The marked decrease of the incidence of goiter was entirely due to the use of iodized salt. The data from which he quotes is from surveys which I made or directed.

Every article written on endemic goiter in Michigan giving the original data of these surveys, also stressed the deficiency of iodine in food and the use of iodized salt. In brief, Michigan has been the proving ground for the prophylaxis of endemic goiter by the use of iodized salt. From 1924 to 1932 more than 90% of the table salt used in Michigan was iodized. All information on the use of iodized salt was published in the same articles from which the data republished by Dr. Greenwald was taken.

It is difficult to understand how anyone could ever have read the literature on Endemic Goiter in Michigan and the use of iodized salt, and then have misunderstood it and misquoted it so completely as is done in this rewriting on the prevention of goiter in Michigan. I can only ask, "Why did he do it?"

His summary represents only personal opinions without scientific data or fair logic to warrant such conclusions.

O. P. KIMBALL
Hanna Building
Cleveland, Ohio
March 4, 1947

LETTER TO THE EDITOR

TO THE EDITOR:

Dr. Kimball objects to my corollaries. I shall discuss them in the order listed in my paper and his letter.

1. In his Harvey Lecture (p. 97), Marine classified simple goiter as a thyroid insufficiency and said that "simple goiter and myxedema . . . are but different stages or degrees of the same nutritional fault." I do not know why we should not draw the corollary that "Goitrous individuals should have low metabolic rates." The fact that they do not was not advanced by me as proof that goiter is not a thyroid insufficiency, for I can think of possible compensatory changes in other organs. Nevertheless, none of these possibilities has been demonstrated nor, so far as I know, even indicated by observations of any kind, clinical or experimental. I maintain my position.

2. "And again, there is no truth in the statement that goiters should contain less iodine than normal thyroid glands." May I quote from Dr. Kimball? (The Thyroid Gland, ed. Amy F. Rowland, Phila., 1922, page

168): "In other words, no functional hyperplasia and, therefore, no goiter can develop, at least in the mammals above mentioned (dog, sheep, ox, pig, rabbit, cat, and man. I.G.), if the iodine store in their thyroids is maintained above 0.1 percent." If, now, the iodine contents of goiters are as great as, or greater than, those of normal glands, and they are, we must assume that the increases in the weights of the glands more than compensates for the low concentrations. I regard such an assumption as entirely unwarranted. It seems to me to be quite obvious that if a goiter is due to a lack of iodine, the goiter should be found to contain less iodine than is present in a normal gland. I maintain that my corollary is logically derived from the proposition and that the fact that the observed facts are not in accord with the corollary is a severe blow to the proposition.

3. Immediately after quoting my corollaries, Dr. Kimball writes: "To even think that the above statements which he calls corollaries should be true shows a complete lack of understanding of simple goiter." Eight lines later, he asserts that Marine and his associates proved my corollary to be true! I do not know to which experiments, by Dr. Marine, Dr. Kimball refers. The only statement I can find is in the Harvey Lecture, pages 105 and 106. There is, however, no mention of iodine-free diets and the dose of iodine given was one milligram per week to each puppy. I submit that this dose cannot be regarded as merely making good a hypothetical deficiency and that the observations do not in any way substantiate the corollary. If Dr. Kimball knows of any experiments by Dr. Marine with iodine-free diets, I wish he would let me know where they were reported. I have not seen any reference to them in any paper by others who have attempted to produce goiter by lowering the iodine intake.

Dr. Kimball objects to my use of the data in his report of 1937. Just what the words "Instead . . . 1935" are intended to mean is not clear. They do not form a sentence. Perhaps some words have been omitted. Dr. Kimball also writes: "From 1924 to 1932 more than 90% of the table salt used in Michigan was iodized." I do not know just what the significance of this is supposed to be. According to Dr. Kimball's own summary of the Michigan census, there were a total of 61,649 children included in the survey. Of these, 9,429 are listed as *never* having used iodized salt. For the entire group of 61,649 children, whether they used iodized salt regularly, occasionally, or not at all, the reduction was, as stated, from 38.6% in 1924 to 8.2% in 1935. It is perfectly true that the Cleveland group that had not used iodized salt for three years showed no such reduction. I said so on page 732 and attempted an explanation on page 733. I have neither misunderstood nor misquoted the data.

The prophylactic use of iodine has not uniformly been followed by a reduction in the incidence of goiter. To the instances of *increases* in the oc-

currence of goiter cited in my paper, I would like to add those cited on page 193 of an article by Hercus and Purves (*Journal of Hygiene, 26,* 182–203, 1936). One observer reported: "In spite of the fairly general use of iodized salt, there appears from the year's figures to be a decided increase in the amount of goitre in all ages in both incipient and small classes." Hercus and Purves themselves observed several instances of goiter in women who used iodized salt (1:250,000) regularly. Dr. Kimball would, I supposed, retort that this amount is inadequate. Perhaps it is, but not because "one milligram per day, from iodized salt" (see his letter, page 2, line 27) is needed to make good a deficiency. A gram or more of quinine a day was once considered necessary to prevent malaria, but not because malaria was believed to be due to a lack of quinine.

"*Post hoc, ergo propter hoc*" is the oldest of the fallacies. The fact that toads appear after a rain is no proof that it rained toads. If Dr. Kimball will trouble to acquaint himself with the history of goiter, he will find that changes in the incidence of goiter as great, or greater than, any he has observed, have repeatedly been reported without any known change in the iodine intake and without the slightest reason for supposing that there was any such change.

In the last sentence of his first paragraph, Dr. Kimball writes: "These references suggest that some one is trying to bring this article to the fore. . . . " Perhaps they do suggest this to Dr. Kimball, but they will scarcely do this to anyone who approaches the discussion with an open mind. I wrote my article and you published it. *Science Service* found it of general interest. Miss Stafford telephoned to me for some additional information and prepared a release and a signed article. *Science Service* publishes hundreds of such releases every year. Newspapers print what the editors consider interesting. There is nothing mysterious about the procedure.

Dr. Kimball asks "Why did he do it?" There is only one answer. Because a careful examination of the literature led me to the conclusion that the "iodine-lack" hypothesis rested on no satisfactory evidence whatever; and was, in fact, contradicted by such evidence as is available. I have no apologies to offer, except to my students whom I had so long misled.

ISIDOR GREENWALD, M.D.
477 First Avenue
New York 16, N. Y.
March 12, 1947

LETTER FROM THE FORMER MANAGING EDITOR

TO THE EDITOR:

This *Journal* has recently published an article written by Dr. Isidor

Greenwald, titled "Is endemic goiter due to a lack of iodine?" [*6:* 708–741 (1946)]. This work of Dr. Greenwald's has been the subject of an adverse Editorial in the *Journal of the American Medical Association* [*133:* 620 (1947)], and in view of the type of comments in that editorial and the fact that the decision for publication of Dr. Greenwald's article was made during my tenure of your present office, it seems appropriate, if you approve, to call to the attention of your readers the following:

When Dr. Greenwald submitted his article for publication the controversial nature of its contents was duly noted, and yet the several experts, whose advice was sought on the question of publication, were in agreement (with one exception) that this scientist deserved an opportunity to present his views on this subject. It is fair to say that while the opinions varied somewhat as to the emphasis that should be placed on the various parts, the current interest in antithyroid substances and the inconsistencies in the existing evidence, of which everyone was aware but which were considerably emphasized by Dr. Greenwald, had something to do with the decision to publish his article.

A lively reaction to the statements of Greenwald would be anticipated, especially by any one who attended the Third International Goitre Conference (1938), at which what seemed to be overwhelming evidence was presented supporting the iodine-lack hypothesis. Yet, even at that conference there was discussion of the information then available on antithyroid substances.

Too few students of goitre seem to be aware of the fact that nearly a century ago a commission was appointed by the French Academy to determine whether iodine deficiency was related to the causes of goitre. This Commission, after a careful study, reported in 1852 that they were unable to relate goitre to iodine deficiency because of inconsistencies in the data. This decision so discouraged scientific studies on the use of iodine in the prevention of goitre that more than fifty years had to pass before progress again could be made.

The Editorial in the *Journal of the American Medical Association* deals too abruptly with the matter, and with one sentence attempts to dispose of the author and his evidence. One wonders whether the writer of the Editorial read the original article as published in this *Journal*, for no reference was cited; there is merely a statement that "This extraordinary folly, unsubstantiated by anything resembling scientific evidence, has been circulated by *Science Service.*"

We all naturally regret that the efforts of the Council on Foods and Nutrition, which has done so much good, may have been in any way embarrassed by this publication, and had any one connected with this been appraised of the state of affairs as presented in the Editorial, undoubtedly

publication could have been delayed. However, it would seem to be impossible for your Editors to prevent for long the publication of a sincere presentation of an opposing viewpoint by a competent scientist merely because an agency had once made a general decision on the subject.

Greenwald did not deny beneficial effects from iodide therapy, but stated in his summary, "The beneficial effects, such as they were, appear to have been due, not to the making good of a deficiency, but to a pharmacodynamic action of iodides." Should this conclusion of his be verified, iodide therapy would remain inescapable until some better method would be discovered.

Your readers will now understand that no matter what were the opinions of the individual editors and the guest referees of the *Journal of Clinical Endocrinology* on the relation of iodine to the cause of simple goitre, they believed that the subject deserved a presentation.

K. W. THOMPSON, M.D.
(former Managing Editor)
154 Upper Mountain Avenue
Montclair, New Jersey
March 13, 1947

Announcements

SCHERING GRANTS TWELVE ENDOCRINE RESEARCH FUNDS

Mr. Francis C. Brown, president of Schering Corporation, of Bloomfield and Union, N. J., has announced that a substantial program of grants in support of medical research studies has been initiated by that corporation, manufacturers of endocrine, x-ray diagnostic, chemotherapeutic and pharmaceutic products.

The use of endocrine preparations in neuropsychiatry will be studied at the Worcester Foundation of Experimental Biology, Worcester, Mass., by Dr. Hudson Hoagland, and at the Montefiore Hospital's Division of Neuropsychiatry, New York City, under the direction of Dr. H. Houston Merritt, professor of clinical neurology at Columbia University, College of Physicians and Surgeons, and Dr. Arnold P. Friedman.

The value of hormones in treatment of internal bleeding and threatened abortion is to be investigated by Dr. Abraham Rakoff at Philadelphia's Jefferson Medical College and Hospital. Drs. Howard C. Taylor, Earl T. Engle and C. L. Buxton, professors of obstetrics, gynecology and anatomy, of Columbia University, College of Physicians and Surgeons, will study sterility in females, and early abortion. Investigation of the relationship of the adrenal gland to pregnancy and toxemias of pregnancy will be directed by Dr. Charles W. Lloyd, associate professor of medicine, at Syracuse University College of Medicine.

Three New York medical schools have been given grants to support studies on endocrines in the field of skin disorders in prepubescent youths, and to develop a new method of administration of estrogens. Dr. Frederick Reiss, associate professor of dermatology at New York University, College of Medicine, will plan the first program; the second at Columbia University's College of Physicians and Surgeons is under Dr. William A. Schonfeld; and the last will be directed by New York Medical College's professor of clinical medicine, Dr. Thomas R. McGavack.

Dr. Harrison F. Flippin, chairman of the committee on chemotherapy at Philadelphia General Hospital, will supervise the study of combined sulfonamide therapy in injections. Dr. Abraham Cohen, of the Philadelphia General and Jefferson Hospitals, will continue his study of the use of gold combined with estrogens and androgens in arthritis.

Dr. Walter M. Kearns, Milwaukee, Wis., continues for another year certain special research studies.

A large grant was given to the Massachusetts General Hospital, Boston, to support that institution's general research program.

"ANDROGENS IN FEMALE" SUBJECT OF NEW 1947 SCHERING AWARD COMPETITION

"The Clinical Use of Androgens in the Female" has been selected as the subject for the 1947 "Schering Award" competition among medical students in the United States and Canada, according to Dr. John N. McDonnell, Director of Domestic Sales and Promotion for Schering Corporation, Bloomfield, N. J. As in previous years, cash prizes of $500.00, $300.00 and $200.00 will be given for the best manuscripts received on this subject. Three judges prominent in endocrinology will select the winning entries. Dr. Norman L. Heminway, head of the Schering Medical Service Department, is chairman of the Schering Award Committee and in charge of the competition.

The "Schering Awards" are offered annually in competition to stimulate the acquisition of further knowledge of endocrinology by medical students, as a contribution to medicine by Schering, world's largest manufacturer of hormones.

Many students from almost a hundred medical colleges will submit their manuscripts for this year's Schering Award Contest which closes July 31, 1947. Even more widespread interest is anticipated in the 1947 "Schering Award" than in previous years.

THE FOURTH INTERNATIONAL CANCER RESEARCH CONGRESS

The Fourth International Cancer Research Congress will be held in St. Louis, Missouri, U.S.A., September 2 to 7, 1947. The Union Internationale Contre le Cancer has accepted the invitation of the American Association for Cancer Research, and the congress will be held under the joint auspices of these two organizations, with Dr. E. V. Cowdry, Professor of Anatomy, Washington University School of Medicine, and Director of Research of the Barnard Free Skin and Cancer Hospital, serving as president of the congress.

Of the three congresses that have been held previously, the first was in Madrid, Spain, in 1933; the second in Brussels, Belgium, in 1936; the third in Atlantic City, New Jersey, U.S.A., in 1939. Due to the recent war, there has been no meeting of the congress during the past eight years.

The State Department in Washington has approved the International Cancer Research Congress, and official invitations soon will be sent to all foreign governments who are to send delegates.

Initial steps in the organization of the congress have been completed. All officers and committees have been appointed and are enthusiastically at work. In addition to the president, Dr. E. V. Cowdry, Dr. J. Godard, president of the Union Internationale Contre le Cancer, and Dr. W. U. Gardner, president of the American Association of Cancer Research, will serve *ex officio* as members of the executive committee.

The following committee personnel have accepted chairmanships:

A. N. Arneson, St. Louis, Missouri—Local Arrangements
S. Bayne-Jones, New Haven, Connecticut—Finance
C. W. Larimore, New York, New York—Exhibits
L. A. Scheele, Bethesda, Maryland—Governmental Liaison
M. G. Seelig, St. Louis, Missouri—Publicity
Shields Warren, Boston, Massachusetts—Program

Headquarters will be at the Hotel Jefferson, St. Louis, where some three hundred rooms will be available for guests. In addition to these rooms, other nearby St. Louis hotels have signified a willingness to make reservations on advance notification by those contemplating attendance at the Congress.

Association Notice

The 29th annual meeting of the Association for the Study of Internal Secretions will be held Friday and Saturday, June 6th and 7th, 1947, in the Viking Room of Haddon Hall Hotel, Atlantic City, New Jersey, preceding the Centennial meeting of the American Medical Association.

Members are urged to make reservations immediately inasmuch as the hotels expect to be filled to capacity. Make your reservations directly with Chalfonte-Haddon Hall advising them of the accommodations you wish. Rates are as follows:

	Chalfonte	Haddon Hall
Single room with bath:	$6, $7, $9	$7, $8, $10
Double room with bath (without ocean view):	$8 and $10	$10 and $12
Double room with bath (side ocean view):	$12	$14
Double room with bath (ocean front):	$14 and $16	$16 and $18

Make your reservations now and avoid disappointment—remember, you can always cancel them at a later date.

Further information regarding the meeting will be forthcoming at an early date.

Abstracts of
CURRENT ENDOCRINE LITERATURE

Editor; D. A. McGINTY. *Collaborators:* A. R. ABARBANEL, F. N. ANDREWS, B. L. BAKER, F. A. DE LA BALZE, ISRAEL BRAM, R. A. CLEGHORN, RUCKER CLEVELAND, C. D. DAVIS, ANNA FORBES, M. B. GORDON, H. S. GUTERMAN, M. M. HOFFMAN, R. G. HOSKINS, C. D. KOCHAKIAN, H. S. KUPPERMAN, H. L. MASON, JANET W. MCARTHUR, THOMAS H. MCGAVACK, A. E. MEYER, K. E. PASCHKIS, A. B. PINTO, J. R. REFORZOMEMBRIVES, E. C. REIFENSTEIN, JR., G. G. RUDOLPH, L. T. SAMUELS.

ADRENALS

CONN, J. W., AND K. P. MATHEWS. Addison's disease in the Negro. *Am. J. Med. Sci. 212:* 404 (1946).

The authors report five cases of Addison's disease in Negroes and thus bring the total number of reported cases in Negroes to 26. They believe that there is undoubtedly a much greater number of recognized cases which have not been reported but that the largest group of cases of Addison's disease in Negroes is not being recognized as such. They believe that it is extremely doubtful that the incidence of Addison's disease in Negroes is smaller than in whites since analysis of their own cases leads to the opposite conclusion. They emphasize that increased pigmentation of the skin, which is the most striking hint to the physician of Addison's disease in whites, is of little or no value in suggesting this possibility to him as he examines the Negro patient. However, marked pigmentation on the dorsal surface of the tongue may be a significant finding. All of the cases of Addison's disease in Negroes reported in the literature upon which a pathological examination was made were found to be due to tuberculosis of the adrenals. One of the authors' cases was due to amyloidosis. From the information at hand, it would appear that idiopathic atrophy of the adrenal cortices (which now accounts for about 50% of all cases in whites) is either non-existent or extremely rare in the negro. The authors point out that this is probably not a valid conclusion. The authors conclude that physicians must be on guard for the recognition of Addison's disease in the Negro, which is in all probability much commoner than the number of reported cases would indicate.—*E.C.R., Jr.*

LEWIS, L. A., AND I. H. PAGE. Method of assaying steroids and adrenal extracts for protective action against toxic material (typhoid vaccine). *J. Lab. & Clin. Med. 31*(12): 1325–1329 (1946).

A method is described for determining the relative protective power of adrenal cortical extracts and keto-steroids against the toxic effects of typhoid vaccine in adrenalectomized rats. The substances to be tested is injected daily or twice daily (depending upon the menstruum) for three days prior to the intraperitoneal administration of 1.33 M.L.D. of typhoid vaccine. One protection unit has been defined as the amount of material per 24 hours which will protect 90 per cent of a group of adrenalectomized rats against the above mentioned dose of vaccine. By this method of assay, the relative potencies of several preparations in units per milligram were determined and found to be

as follows: 11-dehydro-17-hydroxycorticosterone, 5.5; 11-dehydrocorticosterone acetate (natural and synthetic), 3.6; 11-dehydrocorticosterone, 3.1; corticonebenzoate, 1.3; 11-ketoprogesterone, between 0.5 and 3.0; desoxycorticosterone, 0.5; progesterone, less than 0.3; and desoxycorticosterone acetate, acetoxypregnenolone, and methyl androstenediol, all less than 0.1. It is clear from the above that all of the compounds possessing an oxygen atom at C-11 exhibited considerable ability to protect animals from typhoid vaccine. The protective capacity of any given substance closely paralleled its activity as determined by the muscle-work test of Ingle. It seems likely, therefore, that a direct relationship may exist between the ability of these substances to protect against typhoid vaccine and their role in the regulation of carbohydrate metabolism.—*T.H.McG.*

SEGALOFF, A. The effect of diet on the growth and survival of adrenalectomized rats treated with desoxycorticosterone acetate pellets. *J. Lab. & Clin. Med. 31*(4): 482–483 (1946).

Immature, adrenalectomized male rats in which pellets of desoxycorticosterone acetate had been subcutaneously implanted were fed four variations of diet with the following results. No diet contained carbohydrate, but all had adequate types and amounts of vitamins for growth in the rat and U. S. P. XII salt mixture. Group I with crude casein and a fatty acid mixture in addition survived and grew during the experimental period of eight weeks. Group II without the fatty acid neither grew nor survived. Group III with a vitamin-free casein plus the fatty acid behaved similarly to group II. Group IV given a diet with fatty acid supplements but no casein acted as did group II. The authors concluded that dietary carbohydrate is not essential for the survival or growth of adrenalectomized rats treated with desoxycorticosterone acetate; that dietary fatty acids either burn as carbohydrate or permit such rats to utilize protein; and that crude casein contains a factor for growth not found in purified materials.—*T.H.McG.*

SHIPLEY, R. A., AND R. I. DORFMAN. The effect of infection and trauma on the excretion of urinary cortin. *J. Lab. & Clin. Med. 31*(4): 481–482 (1946).

The cold test of Selye and Schenker (modified) and the liver glycogen test of Dobriner et al. were used as qualitative methods of bio-assay for urinary cortin. Values for normal young men and women showed "no obvious differences," but the estimated amount of material present was greater for the cold test than for the glycogen test. Eighty patients with infectious diseases, two following the stress of operative procedure (herniorrhaphy), and three after extensive body burns were test subjects. The urines of all these showed a rise in the output of cortin as compared with the normal. During recovery, there was no evidence of an abnormal depression of cortin values.—*T.H.McG.*

SHIPLEY, R. A., R. I. DORFMAN, E. BUCHWALD, AND E. ROSS. The effect of infection and trauma on the excretion of urinary cortin. *J. Clin. Investigation 25*(5): 673–678 (1946).

Extracts of urine were tested for the presence of cortin-like material by (1) their ability to protect adrenalectomized rats from cold and (2) their capacity for causing the deposition of glycogen in the livers of mice. In both instances, the action was referred to standardized results achieved through the use of known quantities of 11-dehydrocorticosterone (Kendall's compound A). Forty-eight hour lots of urine from each of

17 normal persons between the ages of 24 and 38 years were thus studied, as well as similar specimens from 7 patients with infectious disease, 2 undergoing surgical procedures, and 3 with severe body burns. By the cold test, the normal subjects showed an average of 1.1 mg. of compound A-equivalent per day with a range of from 0.5 to 1.8 mg. By the glycogen test, the average was slightly less than 0.4 mg. of compound A-equivalent with a range of from less than 0.2 mg. to 0.8 mg. Sex made no apparent difference in these results. Five of the 7 patients with infectious disease had an increase in the excretion of cortin during the febrile and early post-febrile stages of their diseases; the other 2 were sick for only a day. Normal levels of excretion occurred throughout late convalescence. During the first 2 to 4 days following herniorrhaphy in each of 2 patients, there was a marked increase in urinary cortin to 10-fold the normal preoperative value (as measured by the glycogen deposition test) with a return to normal by the 6th postoperative day. In the 3 burned patients, distinct rises in urinary cortin occurred during the first 8 days; after the 12th day, the values were again within the range of normal. The authors emphasize the point that "during recovery from stress there was no abnormal depression in output which one would expect in the presence of adrenal exhaustion."—*T.H.McG.*

SPENCE, H. M. AND F. G. THOMPSON, JR. Hormone-producing tumor of adrenal cortex with congenital absence of contralateral adrenal gland. *New Eng. J. Med. 236:* 13 (1947).

A large adrenal tumor was removed to relieve a case of Cushing's disease. The patient went into adrenal crisis after the operation and died 36 hours after from adrenal insufficiency. On autopsy no adrenal gland could be found on the opposite side. The authors considered this as probably due to the depressing effect of the hormones produced by the tumor. The importance of pre- and post-operative therapy to offset the danger of the adrenal insufficiency is emphasized.—*L.T.S.*

WILLIAMSON, M. B. Concentration and properties of the adrenocorticotrophic substance in female human urine. *Proc. Soc. Exp. Biol. and Med. 63*(1): 191–194 (1946).

Freshly voided human female urine, dialyzed urine, and acetone precipitated urinary proteins were tested for adrenocorticotrophic activity in white rats by the methods of Moon, and Sayers, et al. for pituitary adrenocorticotrophins. Normal female urine contained adrenocorticotrophic activity not due to its estrogen content. The active material was nondialyzable and thermolabile and appeared to be a protein. It was similar to pituitary adrenocorticotrophin in its ability to produce adrenal weight increases and to depress the adrenal ascorbic acid level in normal and hypophysectomized male rats.—*F.N.A.*

GENERAL

BARKER, H. B. A detailed report on the weights and weight losses of twenty-four men in Santo Tomas internment camp. *J. Lab. & Clin. Med. 31*(10): 1129–1132 (1946).

During 36 months the average weight loss for 1506 men was 51 pounds with a resultant weight which averaged 70 per cent of the prewar figure. For 1232 women, the loss was 32 pounds with a final weight which was 76 per cent of the value prior to war.

The greatest losses were sustained by the older men and women. Despite a diet yielding less than 1,000 calories and approximately 29 to 30 grams of protein daily, edema was quite uncommon. Although details are not given, the author states that pulse rates were usually slow; and that blood pressures of more than 100 mm. of mercury, and red cell counts of over 4 0 million per cu mm. were exceptional findings among the camp population.—*T.H.McG.*

BRADBURY, J. T. A simplified method for the estimation of sodium. *J. Lab. & Clin. Med. 31*(11): 1257–1261 (1946).

A simplification of the uranyl-zinc method for the determination of sodium in body fluids is described. The original method is based upon the ability of uranyl-zinc acetate to precipitate sodium as a triple salt. When redissolved this triple salt gives a colorimetric reaction directly proportional to the number of uranyl ions present in the solution. The author's modification consists in estimating the loss of such color in the supernatant fluid, and from this calculating the amount of sodium necessary to cause such a withdrawal of uranyl. The method checks well with gravimetric determinations. The author states that "The method can be used when sodium chloride concentrations are as low as 0.5 mg. per cubic centimeter."—*T.H.McG.*

CARR, E. A. A rapid bedside test for the detection of hypoglycemia. *J. Lab. & Clin. Med. 31*(11): 1267–1269 (1946).

This method of determining hypoglycemia depends upon an adaptation of the oxidized bismuth-alkali method of detecting sugar in various bodily fluids. Whole blood is precipitated with copper sulfate and filtered under pressure. A drop of the filtrate is allowed to fall upon a large excess of Galatest (or other similar) powder. If within 45 seconds a definite grey or black discoloration develops, the reaction is considered normal. If such a change in color fails to appear, then hypoglycemia is present. In actual tests, a positive grey or black discoloration occurred in all blood sera containing 53 or more milligrams of glucose per 100 cc. Abnormal reactions were observed in all blood specimens containing 44 mg. per 100 cc. or less. All reagents are stable but the powder must be kept dry. The test is designed to consume not more than 3.5 minutes of time and can be carried out at the bedside.—*T.H.McG.*

CHESNER, CHARLES. Hemochromatosis: Review of literature and presentation of a case without pigmentation or diabetes. *J. Lab. & Clin. Med. 31*(9): 1029–1036 (1946).

An atypical case of hemochromatosis occurred in a 14 year old boy who had been anemic for 6 years and had complained of progressive weakness and fatigue for 6 months prior to admission to the hospital for an upper respiratory infection. A moderately severe, hypochromic, microcytic anemia and a very large spleen were found. The latter was removed. Enlargement of the liver was noted for the first time some 5 months later when he was admitted to the hospital for the third time because of weakness, pallor and severe anemia. Two and one-half months later, he was again admitted for abdominal pain, weakness, fever and exacerbation of the anemia. Clinically the "diagnosis varied from subacute bacterial endocarditis to acute surgical abdomen secondary to diseased gallbladder or appendix." Following postmortem examination, the diagnoses were: "Hemochromatosis with hemosiderosis of the liver and pancreas and generalized hemosiderosis; portal cirrhosis of the liver; recent thrombosis of portal and superior

mesenteric veins with hemorrhagic infarction of the lower three-fourths of the small intestine; atelectasis of the right lower lobe; Ghon tubercle in the lower lobe of the right lung; absence of spleen (surgical removal)." The striking and atypical features of his hemochromatosis included his youth; the complete absence of diabetes and of abnormal pigmentation; the presence of anemia for at least 6 years before other disturbances were noted; and the unusual manner of death with portal and mesenteric thrombosis. The diagnosis was based upon the finding of pigment cirrhosis of the liver and pancreas and siderosis in other organs. Several theories regarding the pathogenesis of hemochromatosis are discussed. The authors do not believe repeated transfusions played any part in their case as a total of 2.75 gm. of iron via transfusion were given to the patient over a period of 9 months whereas at autopsy 47 grams of iron was recovered from the liver alone —*T.H.McG.*

ELLIOTT, J. E. AND P. B. PEARSON. A direct photoelectric method for the determination of serum calcium. *J. Lab. & Clin. Med. 31*(11): 1262–1266 (1946).

The method for the determination of serum calcium is based upon the precipitation of calcium as the oxalate and the photoelectric or spectrophotometric measurement of the amount of potassium permanganate reduced by using an excess of this reagent. The values obtained agree well with those derived by electrometric titration with standard permanganate solution.—*T.H.McG.*

HORVATH, S. M., H. Golden, AND J. WAGER. Some observations on men sitting quietly in extreme cold. *J. Clin. Investigation 25*(5): 709–716 (1946).

Forty-five men with an average age of 20.5 years, and "in excellent physical condition" were subjected to a total of 430 tests at temperatures varying from 1.1° to −40° C. Metabolic rates, skin and rectal temperatures and subjective phenomena were continuously recorded over a period of three hours and compared with control values obtained with the ambient temperature at 22° C. "The heat production in the cold was above basal values during the entire test period. In the −40° C. environment average metabolic increases of 13, 53, and 74 per cent were recorded for the first, second and third hours respectively. The rise in heat output during the first hour could not be explained on the basis of shivering. In the third hour, shivering was present in the majority of the subjects. Neither the role of chemical mediators, nor that of increased muscular tonus, could be clearly delinated, and require additional investigation. The fall in rectal temperatures was moderate, although values of 35.4° C. were occasionally observed. The absolute value was not correlated with the presence of shivering and, therefore, low rectal temperatures could not be considered as the stimulus for shivering." The rectal temperature continued to fall for some time after the subjects were returned to an environmental temperature of 22° C. The greatest fall in the mean skin temperatures (an averaged figure for each individual taken from readings on the thigh, toe, arm, calf, and chest) was observed in the first hour of exposure to cold. However, there was considerable variability in the control figures, and in different subjects during any single test as well as in the same subject on repeated test. At the end of 3 hours the average mean skin temperature with an ambient temperature of −17.8° C. was 27.2° C.; and with a surrounding temperature of −40° C. it was 24.5° C. As would be expected, the decrease in the temperature of the toes was greater than for the other parts of the body,

temperatures below 0° C. being recorded in environments of −23° C. or below—*T.H.McG.*

KESMODEL, K. F. Carcinoma of the breast. *South. Med. Jour. 40*(1): 43–46 (1947).

In a discussion of the palliative measures or therapy that may be used in incurable carcinoma of the breast, testosterone propionate was mentioned as an aid in alleviating the pain. The dose used must be large (3,975 mg. in three months in one patient). The author advised frequent blood chemical studies with particular attention paid to the serum calcium level when large doses of testosterone propionate were used for long periods of time.—*H.S.K.*

LEVINE, E. B., AND A. L. SELLERS. Testosterone in angina pectoris. *Am. J. Med. Sci. 212:* 7 (1946).

The authors have reviewed the reports in the literature on the treatment of angina pectoris with testosterone compounds and have reported their experience with this therapy in 24 male patients referred to them with the provisional diagnosis of angina pectoris. They conclude: 1) Neither testosterone propionate intramuscularly nor methyl testosterone sublingually appears to have any value in the treatment of angina pectoris. 2) Testosterone preparations appear to be of definite value in relieving the chest discomfort sometimes associated with the male climacterium or the similar precordial ache of neurocirculatory asthenia occasionally encountered in individuals in the age group commonly subject to angina pectoris. 3) In their field of usefulness, parenteral administration of 25 mg. of testosterone propionate two or preferably three times weekly is to be preferred to the rather ineffective administration of methyl testosterone sublingually in doses of 10 or 15 mg. daily.—*E.C.R., Jr.*

SHARPEY-SHAFER, E. P. 2-Thiouracil in the treatment of congestive heart failure. *Brit. Med. J. 2:* 888 (1946).

Data are given on 12 cases of congestive heart failure treated with thiouracil to produce hypothyroidism and decreased oxygen consumption. Clinical effects on both low-output heart failure and heart failure with emphysema were good. Along with the decreased oxygen consumption and development of clinical evidences of myxedema, there occurred a decrease in the venous arterial oxygen difference, particularly in the low output group. The work of the heart was not changed in some cases although clinical benefit was observed.—*L.T.S.*

PITUITARY

MILLER, R. A. Pituitary hypothyroidism with impaired renal function. *Brit. Med. J.:* 650 (1946).

A case is reported in which a shrapnel wound in the frontotemporal region caused loss of weight, hypothyroidism, impairment of renal function, and a reversal of the concentration of the day and night urine. These symptoms were interpreted as being the result of pituitary damage, even though there was no permanent cachexia, hypogonadism, or lowering of the blood sugar.—*L.T.S.*

SPAIN, A. W. AND GEOGHEGAN, F. Diabetes insipidus with postpartum pituitary necrosis. A report of two cases. *J. Obst. & Gynaec. Brit. Emp. 53* (3):223 (1946).

Collapse, usually associated with hemorrhage, at childbirth is relatively frequently followed by necrosis of the anterior pituitary. The authors report two such cases in which polyuria preceded death which occurred on the tenth and fourth day postpartum, respectively. Extensive degenerative lesions were found in the posterior lobe of the pituitary in each case. In both, some anterior lobe cells had survived.—*R.A.C.*

YOUNG, F. G. Growth and diabetes in normal animals treated with pituitary (anterior lobe) diabetogenic extract. *Biochem. J. 39:* 515–536 (1945).

Normal dogs, cats, and rats were fed a meat diet just sufficient to maintain a constant body weight under normal circumstances. Daily injections of diabetogenic anterior pituitary extract led to nitrogen retention, a rise in body weight and, in the dog and cat, glycosuria. Analysis of the tissues indicated that protein had been deposited at the expense of fat. The loss of calories entailed by formation of new tissue and glycosuria was more than balanced by an increased oxidation of stored fat. An important action of the extract appeared to be the partial replacement of carbohydrate and protein combustion by that of fat. An equicaloric balance between the oxidation of extra depot fat and the deposition of tissue having the composition of muscle would lead to a substantial increase in body weight. Such an effect accounts for the observed increase in weight. A decrease in fat content and a gain in protein-containing tissue result in a higher mean specific gravity. It is suggested that a knowledge of the mean specific gravity might be helpful in cases of pathologic overweight. It is suggested as probable that diabetes represents the pathologic result of an excessive stimulation of those processes (inhibition of carbohydrate oxidation with enhancement of protein storage and of fat combustion) which normally lead to such deposition of new tissue as is associated with growth.—*H.L.M.*

THYROID

BALZE, F. A. DE LA. Influencia del hipertiroidism sobre la densidad y contenido en proteínas del plasma. *Medicina 6:* 347 (1946).

The author studied the specific gravity and the protein content of the blood plasma in 13 cases of thyrotoxicosis before and after surgery. Postoperatively there was a slow but constant increase in the specific gravity. There was also a rise in the protein content of the plasma which was most pronounced in the most severe cases. The change in protein content was less closely co-ordinated with the postoperative increase in weight, and was not related to the increase in basal metabolic rate after operation. Hemoconcentration seemed to be one of the factors responsible for the increased plasma density. The author suggests that these changes may be etiologic factors in the ophthalmic disturbances of hyperthyroidism.—*F. A. de la B.*

BOROVSKI, M. L. The role of the nervous system in autotransplantation of the thyroid. *Arkhiv. Pat. Anatomii i. Pat. Fizeologii 7* (2): (1941).

The nerve supply of the normal thyroid gland in rats, rabbits, and guinea pigs consists of a complicated nerve network without endings encircling the blood vessels of the interstitial tissue and penetrating the interfollicular spaces. Autotransplantation of

glands in rats is most successful from 1 to 14 days of age, due to the more powerful regenerative capacities of the organism, particularly the nervous system, during this period. Histologically, no change was seen in the nerve fibers of the transplanted gland.

Regeneration of the fibers in transplants begins on the 15th day and is complete by the 45th day. In cases where the transplant does not attach, absorption occurs between the 19th and 21st days. However, if it was attached within 45 days, absorption was never observed. If the gland did not attach, there was a rapid proliferation of new nerve fibers simultaneously with degeneration of the original nerves. The nerve network of the transplant during the absorption period shows vitality and decays partly during and partly after the decay of the parenchyma. This can be explained only on the basis that the nervous system controls degeneration as well as regeneration of the transplanted gland. This work is, according to the author, the first demonstration of nerve fibers in the transplanted thyroid of rats, rabbits, and guinea pigs, and he concludes that the attachment or absorption of the thyroid gland after transplantation is organized and regulated by the nervous system.—Courtesy J. H. *American Review of Soviet Medicine.*

BRIGGS, G. M. AND LILLIE, R. J. Perosis caused by feeding high levels of thiouracil. *Proc. Soc. Exp. Biol. and Med. 61* (4): 430–432 (1946).

Perosis is a common deformity of the leg bones of growing chickens and is known to have been caused by dietary deficiencies of manganese, choline, biotin, nicotinic acid, and perhaps some unidentified factors. A total of 91 day-old chicks were fed a standard ration or the same ration to which thiouracil was added at a level of 0.5 per cent for a period of five weeks. Forty-six of 47 chicks receiving thiouracil developed perosis, as characterized by an enlargement of the tibiometatarsal joint and by a thickening and bending of the metatarsals. The supplementation of the thiouracil-containing ration with manganese, choline, nicotinic acid, biotin, or riboflavin did not prevent the condition. It was suggested that thyroxin may, in some manner, aid in the prevention of perosis under normal conditions.—*F.N.A.*

BURGESS, A. M. Myxedema controlled by thyroid extract for fifty-two years: report of a case. *Ann. Int. Med. 25:* 146–150 (1946).

The clinical history and autopsy findings are presented of a patient who developed myxedema at the age of 35, was put on thyroid at the age of 39 and died when almost 92 years old. This is probably the longest period of successful treatment of myxedema on record. It is especially remarkable in view of the fact that during the last 20 years the patient suffered from hypertensive and arteriosclerotic heart disease.—*J.M.*

CASTILLO, E. B. DEL, GALLI MAININI, C., FINOCHIETTO, R., LUCHETTI, S. E. AND STAFFIERI, J. J. El tiouracilo como tratamiento preoperatorio del hypertiroidismo en 37 pacientes. *Medicina 6:* 221 (1946).

The authors describe their experiences with thiouracil as preoperative treatment in 37 cases (33 women and 4 men) of thyrotoxicosis.—*F. A. de la B.*

FOLDES, F. F. AND MURPHY, ANNA J. Distribution of cholesterol, cholesterol esters and phospholipid phosphorus in blood in thyroid disease. *Proc. Soc. Exp. Biol. and Med. 62* (2): 218–223 (1946).

The distribution of total cholesterol, cholesterol esters, and phospholipid phosphorus was studied in the blood cells and plasma of 7 hypothyroid and 12 hyper-

thyroid humans. Plasma cholesterol, plasma cholesterol ester, and plasma phospholipid phosphorus were significantly increased in hypothyroid patients and only plasma phospholipid phosphorus was significantly decreased in hyperthyroidism. The plasma cholesterol ester / total cholesterol ratio and the plasma cholesterol / plasma phospholipid phosphorus ratio were significantly increased in hypothyroidism and the cell cholesterol / plasma cholesterol, and the cell phospholipid phosphorus / plasma phospholipid phosphorus ratio were significantly decreased. The only significant change in hyperthyroidism was the increase of the cell phospholipid phosphorus / plasma phospholipid phosphorus ratio. The lipid values and the various lipid ratios of both hyper- and hypothyroid patients returned towards normal following adequate treatment.—*F.N.A.*

JACKSON, A. S. Thiouracil will not replace thyroidectomy. *Surg., Gyn. and Obst. 83:* 249–252 (1946).

Thiouracil will supplement, but not supplant, thyroidectomy in the treatment of toxic goiter, in the author's opinion. He regards thiouracil therapy as contraindicated in the management of toxic adenoma, since adenomas are neoplasms, and the patient may later succumb to malignancy or intrathoracic goiter. He deplores the necessity for prolonged treatment with a toxic drug whose capacity to induce long-term remissions is as yet undetermined. Types of cases in which thiouracil makes a distinct contribution to management are: (1) advanced cases of multiple toxic adenoma in which there is no response to iodine; (2) cases of toxic adenoma complicated by such conditions as myocarditis, fibrillation, hypertension, diabetes and decompensation; (3) cases of severe exophthalmic goiter in the very young, the aged, the debilitated, and the decompensated; (4) cases of exophthalmic goiter in which, because of pregnancy, previous nerve injury, infections or other diseases, it may be desirable to delay surgery and yet not continue with iodine; (5) cases of iodine-fast exophthalmic goiter; (6) cases of persistent or recurrent hyperthyroidism.—*J.M.*

LERMAN, J., JONES, H. W. AND CALKINS, E. Studies on two sporadic cretinous brothers with goiter, together with some remarks on the relation of hyperplasia to neoplasia. *Ann. Int. Med. 25:* 677–701 (1946).

Two patients with sporadic cretinism and goiter are presented. The thyroid glands removed at operation were similar in appearance microscopically and showed areas of fetal adenoma, papillary cystadenoma, struma nodosa micro et macrofolliculare, and involution. The similarity of these glands to the thyroids of cretinous pigs whose parents were fed on a soybean diet and to the thyroids of certain patients given thiouracil preoperatively is pointed out. The fragmentary evidence suggesting that neoplasia may be the end-result of extensive hyperplasia is discussed.—*J.M.*

LINNELL, J. W., KEYNES, GEOFFREY AND PIERCY, J. E. Some vulgar errors in regard to goiter. *Brit. Med. J.:* 449 (1946).

The article is a plea for the early surgical treatment of goiter even though it is not patently toxic. The authors discuss 11 errors which they feel are commonly made by many medical men. The first is that apparently nontoxic goiters are harmless. The next three points attacked are the ideas that tachycardia, loss of weight, and elevated basal metabolic rate must be present for the diagnosis of toxic goiter. Under the next three headings the authors attack the ideas that iodine, x-ray, or thiouracil are adequate curative treatments for goiter. The next three points attacked are various objections raised

to surgical removal. The last point which the authors make is that thyroid surgery requires experience. The discussion is general and does not deal with specific data.—*L.T.S.*

MEANS, J. H. Evaluation of the several methods for treating Graves' disease available today. *Ann. Int. Med. 25:* 403–411 (1946).

The relative merits of (1) subtotal ablation of the thyroid, (2) medical treatment with antithyroid drugs, and (3) irradiation of the thyroid by means of radioactive iodine, for the treatment of Graves' disease, are evaluated. The author favors thyroidectomy after preparation with an antithyroid drug in combination with iodine, over prolonged use of an antithyroid drug alone. Judgment regarding the ultimate place of radioactive iodine therapy is withheld pending more extensive and prolonged utilization.—*J.M.*

TRASOFF, A., WOHL, M. G. AND MINTZ, S. S. Fatal agranulocytosis with autopsy following use of thiouracil in case of thyrotoxicosis. *Am. J. M. Sc. 211:* 62 (1946).

The authors report a fatal case of agranulocytosis in a 34 year old man who had been treated for seven months with thiouracil (0.6 to 0.1 gram daily) for thyrotoxicosis. The patient developed acute membranous pharyngitis, meningeal irritation, and succumbed after an illness of three days. At autopsy, the thyroid showed histologically focal hyperplasia, and focal colloid goiter (iodine had been administered), and the bone marrow was hypoplastic. The patient exhibited a high degree of pyrexia, marked irritability, restlessness, and hyperkinetism during the entire course of his hospital stay, which required shackling to restrain him even after the use of morphine and other sedatives. The authors interpret these findings as evidence of an aggravated state of thyrotoxicosis resulting from the infection and suggest that a thyroid crisis contributed to the fatal termination.—*E.C.R. Jr.*